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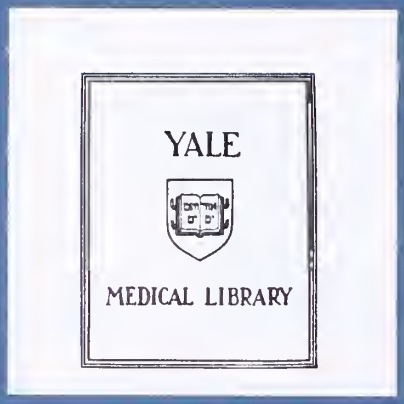
ACUTE TUBULAR NECROSIS - ACID/BASE AND URINARY SEDIMENT CHANGES

Maria Schmidt

1983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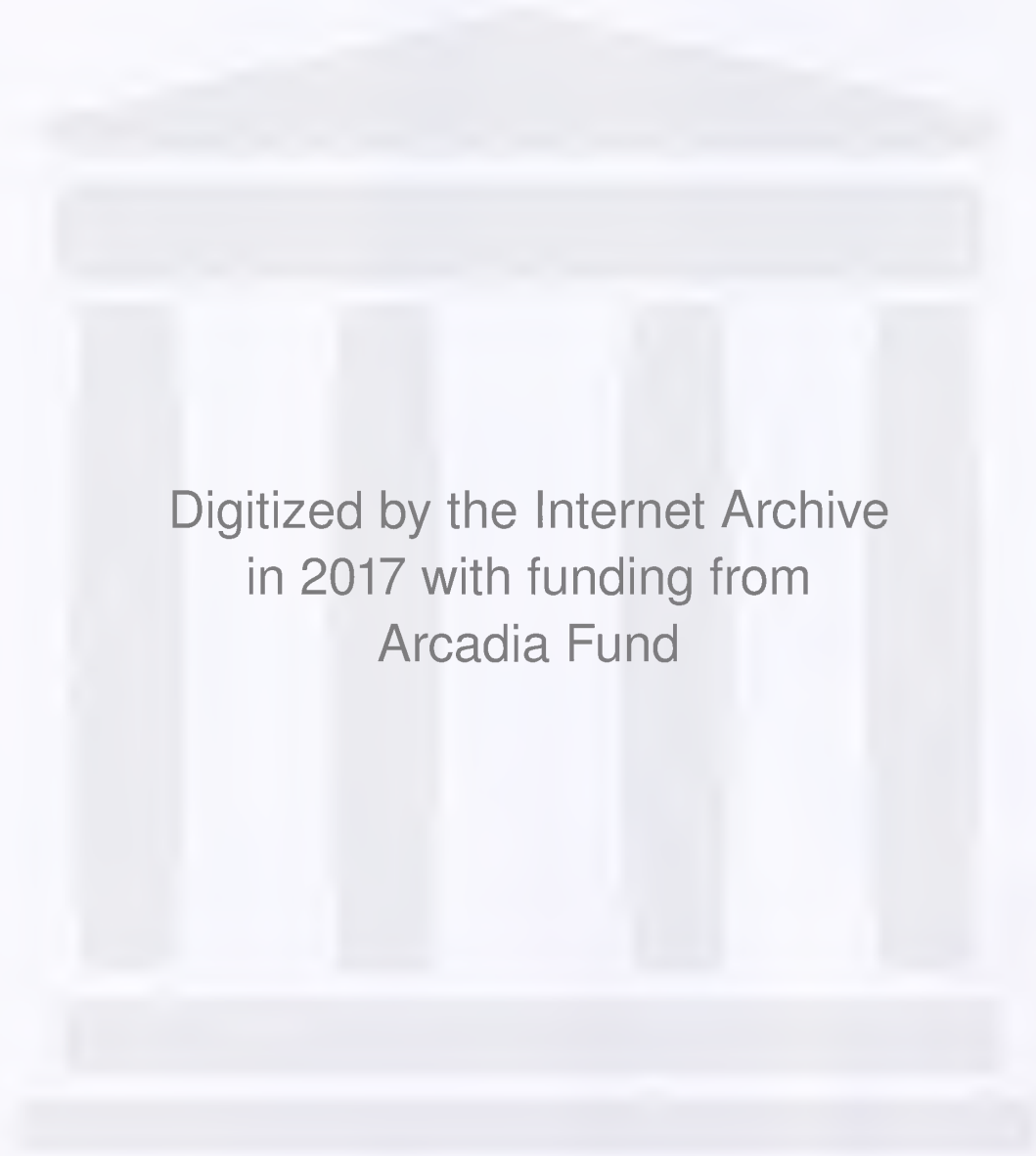
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ACUTE TUBULAR NECROSIS —

ACID/BASE AND URINARY SEDIMENT CHANGES

A Thesis Submitted to the Yale University
School of Medicine in Partial Fulfillment
of the Requirement for the Degree of
Doctor of Medicine

Maria Schmidt

1983

ACKNOWLEDGEMENT

I wish to extend my heartfelt thanks to Peggy Bia, M.D. for teaching, guidance, and encouragement during my medical education at Yale, and for her help and patience in the production of this thesis.

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LIST OF ABBREVIATIONS

ARF	acute renal failure
ATN	acute tubular necrosis
BP	blood pressure
BUN	blood urea nitrogen
CRF	chronic renal failure
creat	creatinine
CT	computerized tomography
Fe_{Na}	fractional excretion of sodium
GFR	glomerular filtration rate
HPF	high power field
IVP	intravenous pyelogram
Na	sodium
NH_4Cl	ammonium chloride
RFI	renal failure index
U	urine
VAH	West Haven Veteran's Administration Hospital
YNHH	Yale-New Haven Hospital

ABSTRACT

Twenty patients with acute renal failure (ARF) were studied prospectively in an effort to characterize the renal acidosis of acute tubular necrosis (ATN), and also to define the diagnostic usefulness of certain tests, particularly the examination of the urinary sediment. 14 patients with ATN were followed during the 3 months of the study. Sequential urine samples were collected and examined for sediment findings, urinalysis, and pH. Additional laboratory data ordered for each patient was analyzed.

The urinary indices commonly cited as useful in the determination of ATN, i.e.: the U_{Na}, the Fe_{Na}, and the RFI, were found to be neither specific nor sensitive enough to be diagnostic without considerable additional data for each patient. The finding of formed elements in the urinary sediment was found to be of little use in distinguishing ATN from other types of ARF in this study, and a benign sediment was noted in over one third of patients (36%).

Results of acid-base studies revealed that in ATN many patients never develop acidemia (55%), many have primary mixed disorders of metabolic acidosis and respiratory alkalosis (55%). Most patients manifest a decrease in serum bicarbonate with a reciprocal increase in the anion gap (93%). The distal renal tubular ability to generate a concentration gradient of hydrogen ions of 100:1 appears to remain intact in ATN.

Poor prognostic indicators demonstrated in this study were oliguria, high anion gap, and multiple inciting insults in ATN.

INTRODUCTION

Acute tubular necrosis (ATN) is a type of acute renal failure (ARF) that cannot be rapidly reversed by specific medical interventions, that usually results in death or complete recovery, and that carries with it a mortality of 20-70%, depending on the etiology. It is believed to be caused by renal ischemia or toxicity, or both, and may occur following a great variety of insults. The exact pathogenesis has not been worked out, but current theories emphasize variable degrees of glomerular vs. tubular dysfunction and have to account for a wide variety of histological changes seen, as well as the potential for complete recovery. A prospective study of 14 patients with ATN is presented here. The emphasis has been on the acid-base status of these patients, as well as the value of the urinalysis as a specific diagnostic test for this entity.

The diagnosis of ATN is most problematic in its differentiation from other forms of ARF, most commonly from prerenal azotemia. Once ARF is established, ATN is essentially a diagnosis of exclusion. In assigning patients to the various groups in this study, standard diagnostic criteria were applied, with an emphasis on the history, the clinical presentation, the hospital course, and certain laboratory data. The criteria used for patient classification are summarized below:

1. prerenal azotemia:
   a) oliguria, defined as urine output $\leq$ 400 ml/day
   b) azotemia
   c) clinical setting consistent with renal hypoperfusion, as seen with intravascular volume depletion, cardiogenic shock, operative interruption of circulation, or pharmacologic vasoconstriction
   d) return of normal renal function within 24-48 hours of correction of the inciting abnormality
   e) typical urinary indices i.e.: $U_{Na} \leq 20$, high U_{osmo}, U/P osmo ≥ 1.2, U/P creatinine ≥ 40, $Fe_{Na} \leq 1\%$

2. postrenal azotemia:
   a) evidence of bladder neck, ureteric, or urethral obstruction, either radiologic or by diuresis following catheter insertion
   b) return of normal renal function within 24-48 hours of correction

c) normal sized kidneys by x-ray to rule out chronicity

3. vascular obstruction: a) renal artery - associated with hypertension, renal artery stenosis, bruits, and fluid retention
   b) renal vein - seen with thrombosis or invasion, associated with significant proteinuria, hematuria, and usually nephrosis
   c) multiple emboli - in the clinical setting of cholesterol or thrombotic emboli, but diagnosis only by biopsy

4. renal parenchymal: a) glomerulopathy - history and laboratory evidence of streptococcal infection or vasculitis, associated 3-4+ proteinuria, red blood cell casts
   b) interstitial nephritis - history of appropriate drug ingestion,e.g.:certain penicillins, furosemide, thiazides, allopurinol, etc.; associated with fever, rash, hematuria, urinary eosinophils
   c) intratubular precipitation - in the setting of myeloma, or with hyperuricemia following cytotoxic drugs

5. ATN: a) a decline in renal function with at least a 2-fold increase in creatinine for at least 3 days
   b) oliguric or non-oliguric ($\geq$600 ml/day), but rarely anuric ($<$50 ml/day)
   c) ARF that is non-responsive to volume expansion, and exclusion of all other etiologies of ARF (1-4,above)
   d) a documented insult directly followed (by $<$48 hours) by a typical course of renal failure, with a rise in serum creatinine $\sim$0.5-1.0 mg/dl/day
   e) typical urinary indices, i.e.: U_{Na} $>$ 40 mEq/L, U/P osmo $<$ 1.2, U/P creatinine $<$ 20, Fe_{Na} $>$ 1%, RFI $>$ 1
   f) known insults defined as:
      - hypovolemia or circulatory insufficiency, with either: systolic BP $<$ 90, orthostatic signs, or decreased central venous pressure; or decreased effective, but increased extracellular fluid volume in patients with cardiac failure, hepatic cirrhosis, or nephrosis
      - sepsis - either a documented bacteremia or a known focus of infection, and associated with it at least one of the following: unexplained fever or hypotension, leukocytosis $>$ 15,000, rigors, or tachypnea

- nephrotoxin - aminoglycoside antibiotics - with high blood levels, simultaneous administration of more than one, long course of administration, or multiple insults
- radiographic contrast dye - as administered for IVP, angiography, CT scanning; especially at risk: diabetics and dehydrated patients
- organic solvent ingestion, e.g. methanol, ethylene glycol
- rhabdomyalysis - traumatic (crush,burns, muscle inflammation) or non-traumatic (drug or EtOH abuse, coma, seizures, exertion); associated with CPK$\geq$4000, gross pigmenturia, pigmented granular casts

While the present study was not primarily directed at establishing diagnostic criteria for ATN, its prospective design made it ideal for re-examination of several commonly performed diagnostic tests, with a primary focus on the microscopic analysis of the urinary sediment. Examination and interpretation of the urinary sediment has traditionally been considered a crucial step in the differential diagnosis of renal disease. Levinsky (19) has claimed that the combination of a characteristic sediment with a high urinary sodium level (U_{Na}) points to ATN, and that this sediment shows a profusion of degenerating cellular casts and granular casts suggesting its diagnosis at first glance .

Casts are cylindrical bodies believed to represent moldings of renal tubules or collecting ducts. Their formation is related to the precipitation of protein and the agglutination of cells and cellular debri. It is felt that low urinary flow, proteinuria, hyperosmolality and acidity all favor this protein precipitation. Casts are made up primarily of a mucoprotein secreted by the distal tubular epithelial cells, Tamm-Horsfall protein. This protein is also found in normal urine in small amounts. Casts are usually not numerous when proteinuria is minimal, and the finding of casts in the urine of normal patients demonstrates their formation in normal tubules as well. Showers of finely granular casts and waxy casts have been found in normal subjects after orthostasis or exercise, and hyaline casts are known to be common in any disease with proteinuria (16). Renal tubular epithelial cells (RTC's) can be distinguished microscopically from epithelial cells from the lower urinary tract, and are found to slough profusely

in many renal diseases including ATN, glomerulonephritis, pyelonephritis, and malignant nephrosclerosis (16).

Since new diagnostic techniques involving radiology, biopsy, and analytic and quantitative urinalysis have achieved prominence in the field of nephrology, it was decided to re-examine the diagnostic usefulness of the findings of formed elements in the urinary sediment, at least as regards differentiation of ATN from other types of ARF. Addis and coworkers previously attempted to quantify the rates of excretion of these formed elements using hemocytometer counts, but demonstrated a very wide range of normal values. This has led to the current opinion that qualitative rather than quantitative examination is more accurate and precise (16).

Obtaining laboratory studies about the chemical composition or the urine is standardly recommended in the management of a patient with ARF (22). Specific values for various urinary indices are described as typical of ATN or of prerenal azotemia, and the calculated fractional excretion of sodium (Fe_{Na}) is felt to be the most reliable index for providing this distinction (22). The standard urinary indices were looked at in the ATN patients here to re-examine their diagnostic usefulness in this patient population.

A major focus of the current study was on documentation of the acid-base status in patients with ATN. Extensive research has been done on the acidosis seen in chronic renal failure (CRF), commonly referred to as uremic acidosis, but little work has focused on its distinction from that occuring in ARF.

Cohen (14) claims that metabolic acidosis always occurs in ARF, but that its magnitude varies widely between patients based on rates of endogenous acid production, extent of residual renal function, and on coexistent extrarenal disturbances. There has been surprisingly little investigation of the nature of the acid-base imbalances, the adequacy of bicarbonate reabsorption, or acid excretion in ARF, however. The one study that looked at acid excretion in ARF (4) found defective ammonium excretion that paralleled the decrease in glomerular filtration rate, implicating glomerular dysfunction in ARF. Urinary acidification was looked at also in that study, but was inadequately tested. Schrier (32) claims that urinary elimination of acid is markedly impaired during both initiation and maintainence of ARF, and he defines this acidosis by the presence of a 1-2 mEq/day decrease in serum bicarbonate levels

and anion gaps greater than 12.

Since the distal renal tubule is responsible for acidifying the urine, i.e.: lowering the urine pH (U_{pH}) from that of the glomerular filtrate (blood pH), it was decided to examine this tubular function in the ATN patients in this study. An attempt was made to identify the presence of metabolic acidosis as well as any other acid-base disturbances in ATN, to try to correlate the bicarbonate and anion gap changes with the acid-base status, and to look at the distal tubular function of urinary acidification, as manifested by the U_{pH}.

Finally, possible associations were looked at between oliguria and various other factors in ATN, specifically outcome, anion gap, and urinary acidification; and prognostic indicators were defined wherever significant mortality differences were noted.

METHODS

I. PURPOSE

To examine patients with ATN to determine:

I. acid-base status
   A. the frequency of metabolic acidosis
   B. the type of metabolic acidosis, anion gap or hyperchloremic
   C. the ability to establish an H+ gradient in the distal nephron (the frequency of distal RTA)

II. the value of certain diagnostic studies
   A. formed elements in the urinary sediment
   B. standard urinary indices , standard urinalysis

II. PATIENT SELECTION

All adult patients consulted on by the Renal services at YNNH and VAH during the 3-month period ending November 7, 1982 were considered for entry into the study. All patients with ARF, defined as a recent decline in renal function marked by at least a 2-fold increase in serum BUN or creatinine, were included. Patients were excluded from this group if there was evidence of chronic renal disease, with a baseline creatinine elevated to at least 3 mg/dl for at least 3 months. Patients were withdrawn from the study after recovery, death, or discharge from the hospital.

III. CLINICAL STUDY

The medical records of all ARF patients were reviewed on entry into the study and followed prospectively through their hospital course. All available data were taken into account, and patient categories of ARF were determined. Specific data recorded throughout the course of the ARF included serum and urine electrolytes, BUN, creatinine, arterial blood gas, fever, BP's, central venous pressures, fluid balance, drainage, respiratory assistance, dialysis, and medications. All tests except the examination of urine were obtained at the discretion of the caring physicians, and the data was recorded by the investigator. Attempts were

made to classify the type of ARF, the inciting event, and to follow the course of each patient, with emphasis on the acid-base status.

Sequential urine samples for examination of pH, sediment, and urinalysis were collected from patients as soon as urine flow permitted. Samples were requested and collected by the investigator, and they were covered and refrigerated immediately if there was any delay between ward collection and laboratory analysis. Only freshly voided samples were used: none had remained longer than 15 minutes at the bedside or had collected in the bag attached to the Foley catheter. All measurements , including microscopic examination, were made in duplicate.

A 15 ml sample was collected for urinalysis and measurement of specific gravity. Protein, blood, glucose, and pH were determined with Labstix reagent strips, and a standard hydrometer or refractometer used for specific gravity determination.

For microscopic examination, 5 ml samples were collected, centrifuged for 3 minutes at 2,000 RPM in a table-top centrifuge, and the supernatant poured off. The pellet was gently resuspended in 0.5 ml of supernatant, and one drop of the mixed sediment then placed on a glass slide with coverslip. Using a standard bright-field microscope, the entire slide was first scanned under the low power objective (10x), followed by closer inspection and counting with the high power objective (40x). Counts were determined for red and white blood cells, renal tubular cells (RTC's), epithelial cells, finely granular casts, hyaline casts, and dirty, brown granular casts (DBGC's). Cast and RTC counts were recorded as:

"numerous" ≥ 1 per 1-10 high power field (HPF),
"many" = 1 per 10-20 HPF,
"occasional" = 3-10 per slide, or
"rare" = 1-3 per slide.

Blood cell counts were recorded as number per HPF, and qualitative notation only was made for the presence of bacteria, crystals, yeast, and debris. Throughout the study, microscopic inspection was performed under the supervision of the attending renal staff for confirmation of recorded formed elements.

Specimens for pH determination were drawn into 100 ul capillary tubes and capped, or 5 ml samples were collected under parrafin oil in glass tubes and measured with either the Radiometer Copenhagen Ionized Calcium or Acid-Base Analyzer.

IV. CONTROLS

Urinary sediment results from patients with ATN were compared with results from patients with other types of ARF.

To determine grossly whether decreased urine flow and oliguria per se affected urine pH, urinary acidification in patients with ARF was compared with that in patients with CRF on dialysis, who were expected to be oliguric. Although patients with ARF and CRF differ in many ways regarding the type and degree of kidney damage, it was anticipated that CRF patients still have intact distal acidification processes. They were chosen as controls to test the hypothesis that a decreased urine flow per se does not adversely affect the tubular ability to establish a H+ gradient. Chronic dialysis patients from YNNH were included if they had: 1) been on dialysis $\geq$ 6 months, 2) had low baseline bicarbonate levels suggestive of acidemia, and 3) had sufficient urinary output to donate a 3 ml sample prior to going on dialysis. One sample was collected from each patient , and collection and pH measurement was performed in the same manner as for ATN patients, described above (III). Serum bicarbonate levels measured the same day as sample collection were recorded.

V. CLASSIFICATION OF PATIENTS

Patients were diagnosed as having ARF prior to inclusion into the study as outlined above. After initial and follow-up clinical evaluations throughout the hospital course, patients were divided into categories of ARF based on standard diagnostic criteria, as summarized in the Introduction, p. 1 -3 . After classificatin as to specific type of ARF, patients were placed into either the ATN group or the group with all other types of ARF.

VI. DATA ANALYSIS

A. Source of data
- urinary measurements generated by the investigator
- additonal data gathered from the medical records

B. Patient course
- graphical presentation of BUN, creatinine, urine output, anion gap, and serum bicarbonate levels for all ATN patients, with anion gap defined as: anion gap = $2(Na) - [(Cl) + (HCO_3^-)]$, and normal range defined as 8-16

C. Numerical indices

- estimated plasma osmolality = $2(Na) + \frac{BUN}{2.8} + \frac{Glucose}{18}$
- U/P osmo = ratio of urinary to plasma osmolarity
- U/P creat = ratio of urinary to plasma creatinine
- $Fe_{Na} = \frac{U/P\ Na}{U/P\ creat}$ (fractional excretion of sodium)
- $RFI = \frac{U_{Na}}{U/P\ creat}$ (renal failure index)
- 'typical ATN values' (Washington Manual, 22):
  $U_{Na} > 40$, U/P osmo < 1.2, U/P creat > 40, $Fe_{Na} > 1\%$

D. Acid-base status

- all blood gas measurements analyzed for the presence of acidemia, defined as blood pH < 7.37, or alkalemia, pH > 7.43, and for the magnitude of the anion gap
- evaluation of each blood gas and associated serum electrolytes for primary acid-base disturbances, with verification of analyses by Dr.M.Bia
- determination of adequacy of compensation or presence of a mixed primary disturbance by application of the following formulas:
  a) for metabolic acidosis, predicted $pCO_2 = 1.5(HCO_3^-) + 8 \pm 2$
  b) for respiratory alkalosis, maximal $\downarrow (HCO_3^-) = (0.5)(\downarrow pCO_2)$, with 18-22 for acute respiratory alkalosis, and 15-20 for chronic

RESULTS

I. PATIENTS

In all, 20 patients were included in the study, 14 with ATN, and 6 with other types of ARF, breakdown as in Table I. The ATN patients were included in the study an average of 9 days, with a range of 1-38 days. The number of days in the study was defined as the period during which urine samples were obtained and the patient was prospectively followed. The period studied was invariably less than the duration of the ATN, entry into the study being determined by the timing with which the housestaff requested a renal consult. Patients with other types of ARF were included only long enough to firmly establish a diagnosis, during which time samples were collected.

II. ETIOLOGY, AGE, MORTALITY

Each patient with ATN was classified as to etiologic insult, and average ages and mortalities were calculated (Table II). The overall mortality was 35% (7/20), and for the ATN subset, 43% (6/14). Three general classes of insults were noted: nephrotoxic, post-ischemic, and multiple insults. The largest number of patients fell into the nephrotoxic group, with 6/14 or 43% of the patients. There were no related deaths in this group. The post-ischemic group, with 3/14 or 21% of the patients, showed a significant mortality of 67%. The highest mortality, however, was found in those patients who had several documented insults, and in whom it was unclear even in retrospect, which of the insults was primarily responsible for the ATN. 5/14 or 36% of the patients were in this group, and the only one to survive was also the youngest patient in the entire study (age 24). The average age of the ATN patient was 60, and among the various etiologic groups the highest average age was seen with the aminoglycoside nephrotoxicity.

III. COURSE

Pertinent data on patient course and patterns of BUN, creatinine, urine output, anion gap, and bicarbonate changes over time is presented in graphic form (Figures 1-14). For each case a brief summary of the hospital course is given (Medical Summaries). The zero point on each graph, Day 0, represents the day presumed to be the onset of ATN. The rate of rise of the BUN and creatinine in all patients is consistent with the diagnosis of ATN, although an accelerated

rate of rise of creatinine is seen in 2 patients (RG,MK), both of whom were extremely catabolic. Of the 13 patients in whom urinary output was measured, 7 (54%) were noted to have at least one day of oliguria early in their course (SB,EC,RG,MK,JM,LP,MS). The mortality of the oliguric patients was 4/7 (MK,JM, IP,MS), as compared to the mortality of 2/7 for the non-oliguric patients (TB,CP). Oliguria was seen with an incidence of 4/5 among patients with multiple insults inciting their ATN. All of the patients who required dialysis were oliguric, and among all the oliguric patients, 3/7 required dialysis. The anion gap and bicarbonate patterns illustrated in the Figures will be presented in Section VI.

IV. URINALYSIS AND URINARY INDICES

Measurement of specific gravity revealed isotonic urine with little variation with time of day, 1.010 ±0.003. Proteinuria, average 1+, was found in 86% of patients, and hematuria, average 1+, was found in 90%. Glucosuria was only found in two patients, one of whom had hyperglycemia at the time (MS), and the other who had a proximal tubular defect (SB).

The commonly quoted urinary diagnostic indices were examined in the ATN patients, and their values compared with the characteristic values quoted in the Washington Manual (Methods,Data Analysis). The calculated indices are presented in Table III. The RFI was also examined, since it has been shown by Miller (23) to be diagnostic in patients with elements of both prerenal failure and ATN in whom the other indices do not fall within the typical guidelines. The U/P BUN was not looked at, because U_{BUN} was rarely ordered by the housestaff. The infrequency with which U_{creat} was ordered also made it impossible to calculate U/P creat, Fe_{Na}, or RFI in 8/14 patients.

The values listed in Table III were obtained an average of ten days after onset of ATN, but ranged from 1-24 days. The day presented in each case was that on which the most indices were calculable. Of the patients who had more than one urinary index with at least one value atypical for ATN (WB,EC,JM,MS,HW) the Fe_{Na} and RFI were calculable in three (WB,EC,MS). In only one of these (EC) were the Fe_{Na} and RFI then consistent with ATN. Of the two patients with atypical values (WB,MS), one was cirrhotic. The other patient(WB) had all calculable indices atypical for ATN on the day presented, Day 5, but also had laboratory evidence of recovery of renal function by this day with falling BUN, creatinine, and a brisk diuresis (Figure 3).

V. URINARY SEDIMENT

The results of examination of the urinary sediment, often quoted as useful in the diagnosis of ATN, were looked at in all ARF patients in this study. Microscopic findings in the 14 ATN patients were compared with those of the 6 patients with other types of ARF (Table IV). Dirty brown granular casts were considered synonymous with coursely granular or dark or pigmented or broad or brown casts, as they have been variously called in the literature. No significant differences were noted in the finding of DGBC's (50% vs. 67%) or RTC's (50% vs. 33%) between the ATN and other ARF patients, respectively. There were also a significant number of ATN patients in whom neither DBGC's nor RTC's were found (36%), and this finding was twice as common in the ATN group as in the other group. The finding of hyaline casts or finely granular casts was not significantly different in the two groups (not included in Table VII). The results of sediment examination in these 20 ARF patients suggest that it is minimally predictive in differentiating ATN patients from other causes of ARF.

VI. ACID-BASE

A. Overall Disturbance

Arterial blood gas results were obtained in 11/14 patients and were recorded each day during the study. In only 5/11 (45%) was systemic acidemia present significantly throughout the course of renal failure. All of the ATN patients had low bicarbonate levels, and 9 of these 11 had anion gaps that were abnormally elevated (Δ 16). In an attempt to explain the lack of acidemia in the majority of the patients, analysis of the predominant acid-base disturbance was performed in each patient. Sequential blood gases were reviewed, and for each patient the most persistent disturbance overall was determined (Table V). Primary disturbances were defined by application of standard formulae (p. 9).

Of the 11 patients with blood gas analyses, 6 (55%) were shown to have primary disturbances of mixed metabolic acidosis and respiratory alkalosis, 3 of pure respiratory alkalosis, and 2 of pure metabolic acidosis. It is conceivable that some of the patients who by blood gas data were interpreted as having respiratory alkalosis, may in fact have had mixed disturbances, as their histories were consistent with this; however, this could not be definitively proven with the available data. For detailed notes on acid-base results, day by day, refer to Appendix I.

Respiratory alkalosis was seen in 9/11 (73%) of ATN patients. Possible primary causes of this disorder were found in each patient, and these possible etiologies are listed in Table VI.

B. Anion Gap

Serum bicarbonate levels were depressed (< 25 mEq/L) in 13/14 (93%) of the ATN patients through the major part of each course. As well, there was a reciprocal relationship between the changes in the bicarbonate levels and in the anion gap levels (Figures 1-14). This graphical pattern was also seen in those patients who maintained anion gaps within the normal range throughout. This suggested the possibility of some degree of metabolic acidosis in all of the patients, although the magnitude of the anion gaps alone might not indicate this. In addition, very high anion gaps (30, 28.5) were found in the 2 patients with pure primary metabolic acidosis out of the 11 patients with blood gas analyses (SB,CP, respectively). Another 2 were noted to have normal anion gaps throughout, one with a mixed disturbance. In total, 5 out of the 14 patients had normal anion gaps. Among all ATN patients, the anion gaps of the oliguric patients tended to be higher than those who were never oliguric, averages 26 vs. 16, with ranges of (19-35) vs. (12-19), respectively.

The most likely cause of the anion gap elevation is uremic metabolic acidosis with retention of phosphate, sulphate, and other metabolic acid anions, although other known causes of anion gap elevation were present in all of the patients. These interventions and complications are listed in Table VI, and they may have contributed to the anion gaps by the accumulation of lactate, acetate, and citrate anions. As well, respiratory alkalosis alone causes a slight elevation of the anion gap due to alkaline stimulation of metabolic enzymes, but usually only to 14-16, and never > 20. No anion analysis was performed as part of this study, but the poor predictive value of the anion gap in differentiating the various acidoses has been previously shown by Gabow (9).

C. Urine pH

Urinary pH was measured in ATN patients in order to assess the tubular ability to secrete H+ and to generate a pH gradient between urine and blood in ARF. Samples were generally collected from patients once a day, although occasionally twice daily or once every two days. There was a range of 0-16 samples collected from each patient, this variation determined by individual urine output, rate of

recovery, death, patient cooperation, and presence of appropriate blood gas data. No samples were collected from a patient on the day of dialysis. All patients except one (JM) were able to spontaneously lower their U_{pH} below 5.5 when sampled randomly during the first 2 weeks of ATN (Table VII). The average sample was collected 7 days after onset of ATN. This result established the physiologic ability of most patients to generate at least a 100-fold gradient of H+ concentration across the renal tubular epithelium.

Since it is known that urinary pH varies widely over the course of the day and is influenced by many factors, including diet, it was necessary to define a testable stimulus. We looked for patients with acidemia in order to next evaluate the functional ability of urinary acidification. An appropriate stimulus was defined as a blood pH $<$ 7.37, and an appropriate response was defined as a $U_{pH} <$ 5.5, the parameters previously used by Wrong and Davies (39). Samples were only used if they were collected and analyzed within 4 hours of a blood gas measurement, and only if the blood pH revealed appropriate stimulus for acidification. Systemic acidemia was only repeatedly present in 5 patients, 2 of whom had pure metabolic acidosis (SB,CP), and 3 of whom had mixed primary disturbances (JM,IP,MS). These were therefore the only 5 patients in whom an appropriate stimulus was established for testing the functional ability of urinary acidification. Of these, 3 lowered their U_{pH} and 2 did not (SB,JM). While the number of patients appropriately stimulated by physiologic acidemia was small, the results suggest that the ability to maintain at least a 100:1 H+ concentration gradient between urine and blood is intact in ATN. Non-acidemic patients were not acid-loaded, as it was not considered ethically correct to do so for this study.

Patient SB was considered atypical in that her acidosis may have represented a proximal RTA (renal tubular acidosis), although initially on admission she was able to lower her $U_{pH} <$ 5.5. After dialysis was discontinued, her serum bicarbonate fell, and on Days 33-45 averaged 14.3 mEq/L (range 6.6-19), and was accompanied by an average blood pH of 7.29 (range 7.29-7.31). During this time, her U_{pH}'s were consistently $\searrow$ 5.5. The next appropriately acidified urine was not seen until Day 48, with U_{pH}=5.25, blood pH=7.31, and serum bicarbonate=14.9. This suggests appropriate distal tubular acidification as a result of a sufficiently low filtered bicarbonate to allow for complete proximal tubular bicarbonate reabsorption. Her failure to acidify the urine despite significant acidemia until her serum bicarbonate fell below 15, supports a diagnosis of proximal RTA in this patient.

Additional definitive tests that would have documented proximal tubular dysfunction in this patient were not done; however, glycosuria was present as screened for in this study, and it rose as high as 3+. In summary, this patient's findings were considered atypical for ATN, and her proximal tubular defect that became apparent over the course of renal failure may be specific to her toxic ingestion of ethylene glycol.

After obtaining the results of urinary acidification in ATN, an acute renal disease, it was decided to compare them with findings in a chronic, end-stage disease such as CRF. Most patients with CRF have low, if any urine flow; it had been noted that the one ATN patient who clearly showed impaired urinary acidification (JM), had been oliguric at the time. An attempt was made to look for any possible relationship between low urine flow and defective renal tubular acidification in acute and chronic disease groups.

10 CRF patients were included in this part of the study, all of whom had low serum bicarbonate levels (below 20, chronically, and on the day of the study), and the urine samples were collected prior to going on dialysis. It is likely that the patients were acidemic, although no blood gas measurements were obtained in these patients, and therefore actual pH documentation is lacking. However, Weller (38) previously studied the acid-base balance in 10 uremic patients (9 with CRF) and found all to be acidemic before dialysis, with pH's averaging 7.20 (range 6.9-7.37) and bicarbonates averaging 12.6 (range 4.0-21.7). Schwartz (34) also demonstrated a good correlation between decreasing bicarbonate levels and falling pH's in 3 CRF patients following discontinuation of alkali therapy. It has also been shown repeatedly that CRF patients are in positive acid balance (21). For the purpose of this study, the CRF patients were considered to probably have an adequate stimulation for urinary acidification before dialysis. Of the 10 patients, only 3 were able to acidify their urine appropriately (Table VIII).. This represents loss of the ability to generate a H+ gradient in most of these patients. Of the 10 patients, 3 were known to be oliguric (RL,SM, WW) as defined by a daily urine output $<$ 400 ml, and of these oliguric patients, 2 were able to acidify their urine appropriately. Despite the small number, the data do suggest that low urinary flow per se does not hinder the generation of the H+ gradient.

DISCUSSION

I. PATIENTS, ETIOLOGIES, MORTALITIES

The value of any study relies heavily on the number and selection of the subjects involved. The small number of patients in this study, 20 in all, is a somewhat limiting factor. A large emphasis was placed on patient classification, however, and the careful selection of the 14 ATN patients may partially offset this. The ATN group is felt to be representative of the true incidence at YNNH and VAH at the frequency with which the diagnosis is suspected by the house-staff, as a renal consult is then standardly requested here. The incidence of ARF due to prerenal azotemia is probably less well representative of its true incidence, especially as a proportion of the total ARF population. This under-representation is due to its high incidence and typical ease of management in the hospital setting. Thus, patients were generally not available for study if the responsible housestaff considered a renal consult unnecessary.

Results of the breakdown of ATN patients in Table I is comparable in some aspects with those from a recent, large study of 143 ATN patients by Rasmussen (28). The overall mortality in this study is similar to the other (43% vs. 53%), but the breakdown in terms of etiologies is somewhat different. In this study, post-ischemia (hypotension) is lower (21% vs. 33%), aminoglycosides much higher (21% vs. 1%) , radiocontrast dye higher (14% vs. 1%), and the incidence of multiple insults was lower (36% vs. 65%). In the current study, it was of interest that the nephrotoxic group was the largest group, and that 5 of these 6 patients' insults were iatrogenic in origin. The much lower incidence of the nephrotoxic etiology in Rasmussen's study (7% vs. 43% here) may reflect differences in medical practice, e.g. in the use of aminoglycosides and radiologic studies between the two hospitals or the two countries (Australia vs. USA).

II. URINALYSIS, URINARY INDICES

The urinalysis findings of the present study are similar to those reported in the literature for ATN patients. In a large study by Swann (36) isotonic urine was found, and Schrier (33) reports 1-2+ proteinuria and microscopic hematuria, all comparable with the results here.

The results of urinary index calculations from Table III reveal an overall insensitivity in identifying the ATN patients of this study. Only the U/P osmo was characteristic in 90% of patients. The small number of indices calculable for the 14 patients precludes many conclusions comparing their individual usefulness. It points out, however, the infrequency of their routine application at this institution.

Though the urinary indices are quoted as useful in identifying patients with ATN, it is conceivable that they are more useful in excluding other diagnoses, such as prerenal failure, in the setting of ARF. While specificity was not studied here, as only indices in ATN patients were examined, it is known that values characteristic of ATN (ie. high U_{Na}, RFI, and Fe_{Na}) are also seen in CRF, obstructive ARF, glomerulopathy, and after diuretic therapy, implying a low specificity for ATN.

Levinsky reports a low U_{Na} to almost never be associated with ATN (20), and Miller reports a $U_{Na} < 20$ to be highly suggestive of prerenal azotemia (23). The U_{Na} may be more useful in ruling out rather than ruling in ATN. The only patient in this study with a value $<$ 20 had cirrhosis.

The Fe_{Na} and RFI have been cited as useful in distinguishing patients with other indices in the 'gray zone' between characteristic ATN and prerenal values. This situation only applied to three patients in this study, only one of which thereafter had characteristic ATN values for these indices (EC). The Fe_{Na} was first applied by Espinel (6) to differentiate prerenal from ATN patients, and Miller (23) later reported the RFI to be equally useful in distinguishing these two diagnoses. It is known, however, that a low Fe_{Na} is not specific for prerenal failure in patients with glomerulopathies and cirrhosis, and the results of this study suggest that neither index is highly sensitive nor specific in the diagnosis of ATN without considerable additional data.

III. URINARY SEDIMENT

Examination of the urinary sediment has been widely cited as an aid in the differential diagnosis of ARF. Levinsky (20) reports the first sample examined by a nephrologist to be characteristic 70-80% of the time. He found hyaline and finely granular casts in the absence of coursely granular casts to be characteristic of prerenal failure, and he calls the ATN sediment "characteristic to the experienced observer" with DBGC's and epithelial cells, both free and in casts. Schrier (32) also reports finding few formed elements, or at most hyaline casts, in prerenal and postrenal failure and "almost never" seeing a normal sediment in ATN. He describes finding brown, cellular, casts and numerous RTC's $\searrow$ 75% of the time.

The findings of this study differ from those of Levinsky and Schrier. While either RTC's or DBGC's were seen in the majority of ATN patients (64%), the finding of both together only occured in 4/14 (29%), clearly in contrast to Schrier's 75%. The finding of similar casts as well as RTC's in patients with other types of ARF makes any finding in ATN less specific. The high incidence of completely normal sediments in ATN patients (36%) contradicts the view about never seeing a normal sediment. In fact, a critical view of the value of the sediment has been expressed previously by Oken (27), who claimed that the sediment is usually benign, and that broad casts, formerly considered pathognomonic of ATN, may be seen in any oliguric state, signifying only very slow flow through the distal nephron segments. Although the other ARF group studied here is not representative of the entire non-ATN ARF population, the results of this study call into question the diagnostic value of this microscopic exam in the evaluation of ATN.

IV. ACID-BASE STATUS

A. Overall Disturbance

Analysis of primary acid-base disturbances was initiated in the ATN patients in order to determine the incidence of metabolic acidosis and acidemia. Metabolic acidosis has been called an "invariable result" of ARF by Cohen (14) and a "regular accompaniment" by Schrier (32), due to the inability to eliminate the nonvolatile organic acids of endogenous metabolism, phosphoric, sulphuric, and mixed organic acids. The fall in plasma bicarbonate and the high anion gap seen in ARF are attributed to it, and the term "uremic acidosis" is commonly applied. There is usually no distinction made between the acidosis of CRF, which has been studied extensively, and that of ARF, which has received minimal investigation.

Metabolic acidosis is not necessarily marked by acidemia or by a low serum bicarbonate level, since an offsetting process may coexist to normalize the pH, such as respiratory alkalosis.On the other hand, a coexistant metabolic alkalosis could normalize the bicarbonate, making the recognition of metabolic acidosis particularly difficult. There may be no evidence remaining except for the history and perhaps an elevated anion gap, as for instance with the vomiting acidotic patient. To complicate matters further, the anion gap is not truly diagnostic of metabolic acidosis, as it may be elevated for other reasons, and it is not elevated with certain types of metabolic acidosis, such as the hydrochloric variety, or when processes coexist to lower it.

The finding in the majority of the ATN patients (55%) of mixed metabolic acidosis and respiratory alkalosis as a primary disturbance was unexpected in this study. Metabolic acidosis with compensatory respiratory alkalosis has been described in CRF patients in several studies previously, (37,21), manifested by low pCO_2, low bicarbonate levels, and yet normal or even frankly alkaline blood pH's. The respiratory response to acidosis in CRF was shown by some to be no different than that in normal controls administered an acid load (18), or no different than that seen in other metabolic acidoses of equal severity (1). However, Martinez-Maldonado have suggested that the respiratory response might not be regulated by the systemic bicarbonate balance, but instead be a direct uremic alteration of the ventilatory threshold (21). Primary respiratory alkalosis accompanying metabolic acidosis in ARF or ATN has not been reported previously in the literature, but as demonstrated here, appears to be frequent. There

were various known causes of respiratory alkalosis in all of the ATN patients, as presented in Table VI. However it is also conceivable that the respiratory disturbance might be triggered centrally by the uremia itself, as was suggested in CRF, though there is no evidence at present that the processes are the same in CRF and ARF.

B. Anion Gap, Bicarbonate

Acidosis develops in renal failure when bicarbonate is consumed by the retained metabolic acids over the renal tubular capacity for generating bicarbonate, that is, excreting H+. The retention of anions is a function of reduced GFR, and is unrelated to the ability to resorb bicarbonate, per se.

Regarding anion retention in CRF, Cohen claims (14) that with creatinine levels $\geq$ 4 mg/dl there tends to be an elevated anion gap, but that it is not predictably related to the decrease in bicarbonate as it is in the other organic acidoses, but merely reflects the insufficient glomerular filtration. Brenner adds (24) that there is a phase of generalized renal disease where the acidosis shares characteristics of both high and normal anion gap acidoses, and that this occurs when tubular damage is proportionally worse than glomerular. These concepts refer primarily to CRF.

ARF is generally considered an acute shutdown of renal glomerular and tubular function. The glomerular dysfunction with decreased filtration of organic anions is manifest in the elevated anion gaps seen in 64% of the ATN patients in this study, although other factors may have contributed as well, as listed in Table VI. The finding of normal anion gaps in 36% of the patients is not necessarily inconsistent, and might even be artifactual, secondary to hypoalbuminemia in some patients. Emmett and Narins (5) have pointed out the importance of looking for offsetting processes (that cause anion gap depression) when normal anion gaps are seen in the face of renal failure.

Renal tubular dysfunction probably occurs concomitantly with the glomerular dysfunction in ATN, as indicated by histological findings revealing tubular necrosis. It is conceivable, as noted by Brenner, that the finding of normal anion gaps in some patients may represent proportionally greater tubular than than glomerular dysfunction; however, extrapolation from CRF to ARF based on

this result alone is unjustified. The measurements of U_{pH} < 5.5 in this study, establishing a 100:1 H+ gradient, suggest that at least the distal tubular function of urinary acidification remains intact, however, in ATN. Although 93% of patients had subnormal bicarbonates, this probably represented compensation for the primary disturbances of respiratory alkalosis and metabolic acidosis, rather than relating to any renal tubular acidifying defect.

A normal anion gap may, however, be a good prognostic indicator in ATN, as was demonstrated in this study by a marked difference in the mortalities of the normal and high anion gap patients (0 vs. 67%). In addition, the association between high anion gaps and oliguria suggest the possibility that the anion gap elevation reflects the degree of renal dysfunction in ATN.

High anion gaps are commonly considered markers of metabolic acidosis. The finding in this study of the highest anion gaps occuring in the patients with pure disturbances of metabolic acidosis, as well as normal anion gaps in the patients with the least mortality, supports a correlation between degree of metabolic acidosis and severity of illness in patients with ATN. The presence of this metabolic acidosis is masked to a large degree by concomitant acid-base disturbances, as well as probably by interventions and complications, and in all of these patients was best manifest by the pattern of anion gap and bicarbonate changes.

C. Urine pH

Measurement of U_{pH} in this study revealed normal maintainence of the distal tubular H+ secretory ability in ATN, insofar as the generation of a H+ concentration gradient of ≥ 100-fold between urine and blood was confirmed. The only previous study that has looked specifically at urinary acidification in ARF was DeLuna's (4). In that study of 6 ARF patients, it was concluded that 2 had abnormally high U_{pH}'s. In only one was there documentation of systemic acidemia, however, so that appropriate stimuli for urinary acidification may not have existed in the others. The findings of the present study suggest that tubular H+ secretion remains functional in ARF. Although patients were not acid-loaded in this study because of ethical considerations, there was documentation of appropriate physiological stimuli (systemic acidemia) in 5, and the remaining 9 patients were able to spontaneously generate a 100-fold H+ gradient across the renal tubular epithelium. Thus, the ability to build a gradient was present in 14/15 ATN patients, although appropriate responses to

documented stimuli were only elicited in 3/5. Nonetheless, results strongly support intact distal tubular acidification processes in ATN.

In CRF, previous studies have demonstrated the ability to decrease urinary pH below 5.5, and Schrier claims that U_{pH} should be reducible "right to the very end" (33). Kleeman (11) administered an acid load to 45 CRF patients and found all to achieve progressively lower U_{pH}'s, finally reaching pH's 4.8-5.5 after either spontaneous progression of acidosis or administration of NH_4Cl; Wrong (39) administered NH_4Cl to 9 CRF patients and found U_{pH}'s $\leq$ 5.5 in 8/9, as well as finding $U_{pH} \leq$ 5.3 on 6/8 random urine samples from CRF patients; and Simpson (35) found a mean U_{pH} of 5.99 in 10 CRF patients randomly sampled (with blood bicarbonates averaging 18.9), not significantly different than his 11 normal controls. None of these patients were on dialysis.

The results of the 10 random samples obtained in this study from CRF patients differ from those of previous studies. The average U_{pH} of these 10 patients is higher than that of the 10 reported by Simpson (6.6 ±0.97 vs. 5.99 ±0.42), but shows some overlap, and the finding of $U_{pH} \leq$ 5.5 was seen less often here than was seen by Wrong on random urine samples (30% vs. 75%). The difference in these results might be explained by differences in the degree of CRF in the patients in the two studies. The older studies were done before the era of dialysis, and the current study was done on dialysis patients, whose degree of renal impairment must be even greater than that usually seen in earlier studies.

The fact that Kleeman, Schwartz, and Wrong were able to acid-load their patients, and that appropriate urinary acidification was shown, established the tubular H+ secretory ability in those CRF patients. The finding in this study that 6/7 (86%) of oliguric ATN patients could spontaneously generate a 100:1 H+ gradient, and that 2/3 oliguric ATN patients could acidify appropriately under physiological stimulation (IP,MS), as well as 2/3 oliguric CRF patients when randomly sampled, argues that low flow, per se, may not disrupt distal tubular H+ concentrating ability in either CRF or ATN.

CONCLUSIONS

Urinary indices and examination of the urinary sediment are commonly cited as useful diagnostic tools, but none of the findings cited as typical for ATN are very specific, as demonstrated in this study. In terms of diagnostic usefulness, the history and clinical course are primary, and these diagnostic tests are useful adjuncts only in their context.

In this study, the acid-base status of ATN patients was investigated. Metabolic acidosis was not the predominant acid-base disorder in most patients, although it was prominent in some of the sickest patients. Although there was at least some evidence of metabolic acidosis in all patients, respiratory alkalosis was found in most patients as well. Surprisingly few patients were acidemic during their renal failure, and this may have been a result of the concomitant alkalotic disturbances. It is also conceivable that it is attributable to the medical management of these patients, since many were on ventilators.

Distal renal tubular function in ATN was assessed by the ability to generate a H+ gradient between urine and blood. This tubular function appears to be intact in ATN, at least as far as establishing a 100:1 concentration gradient.

The parameters noted in this study to be associated with poor outcome were oliguria, high anion gaps, and multiple inciting insults.

FIGURE 1: TB

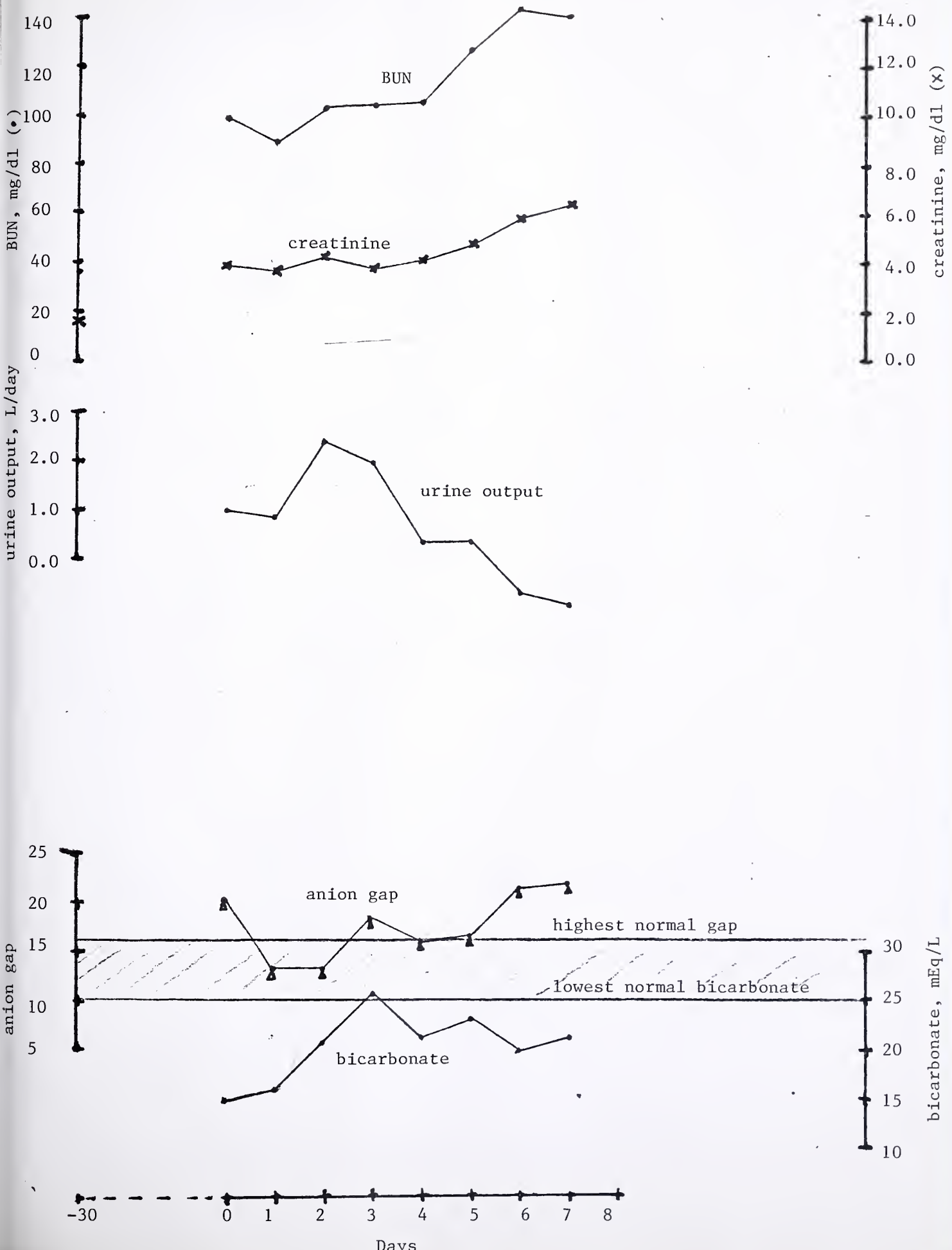

BUN, mg/dl (•)
140
120
100
80
60
40
20
0
BUN
creatinine
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
creatinine, mg/dl (x)
urine output, L/day
3.0
2.0
1.0
0.0
urine output
anion gap
25
20
15
10
5
anion gap
highest normal gap
lowest normal bicarbonate
bicarbonate
30
25
20
15
10
bicarbonate, mEq/L
-30
0
1
2
3
4
5
6
7
8
Days

FIGURE 2: SB

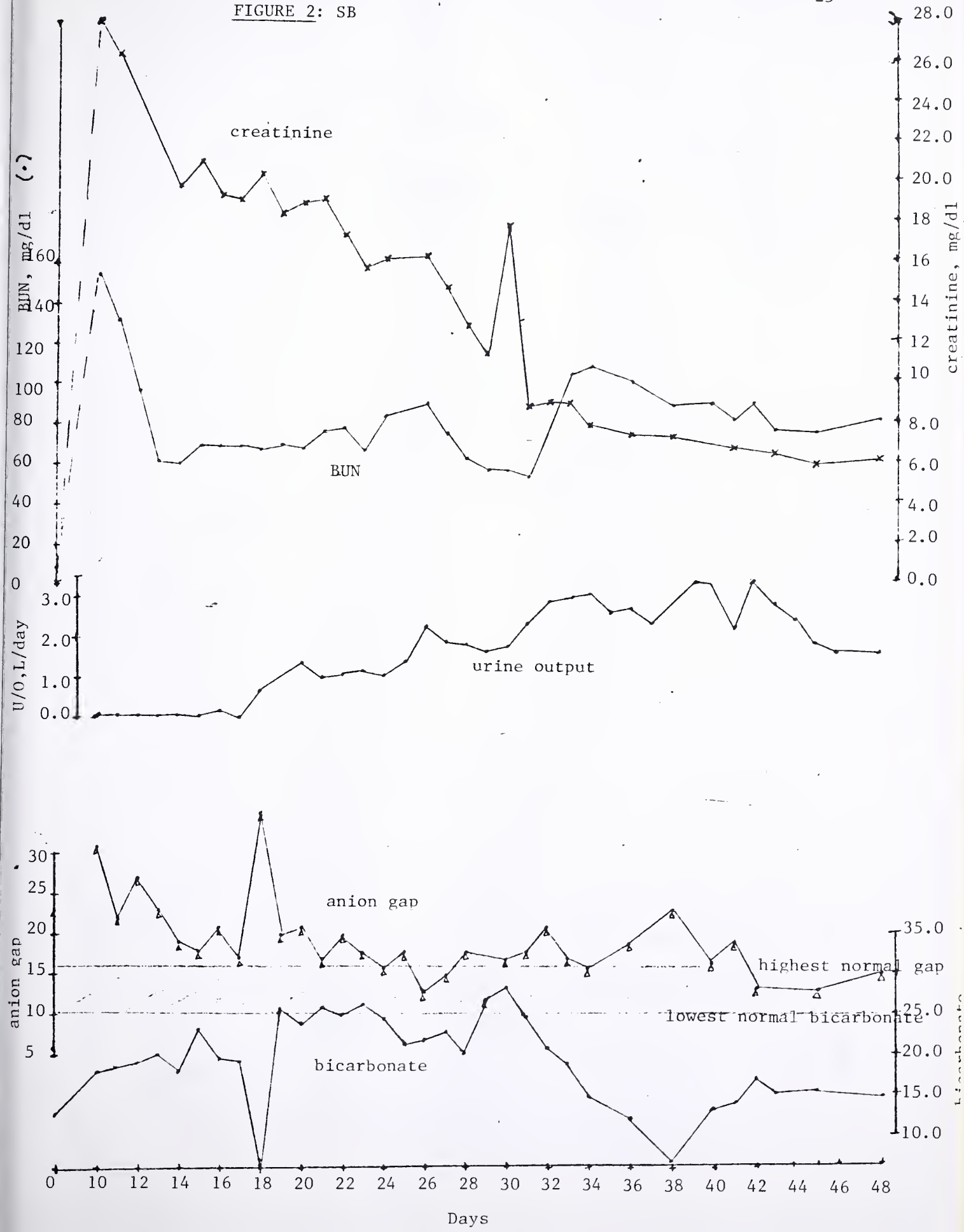

creatinine
BUN
urine output
anion gap
bicarbonate
highest normal gap
lowest normal bicarbonate
BUN, mg/dl (•)
creatinine, mg/dl
U/O,L/day
anion gap
Days
0 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48

FIGURE 3: WB

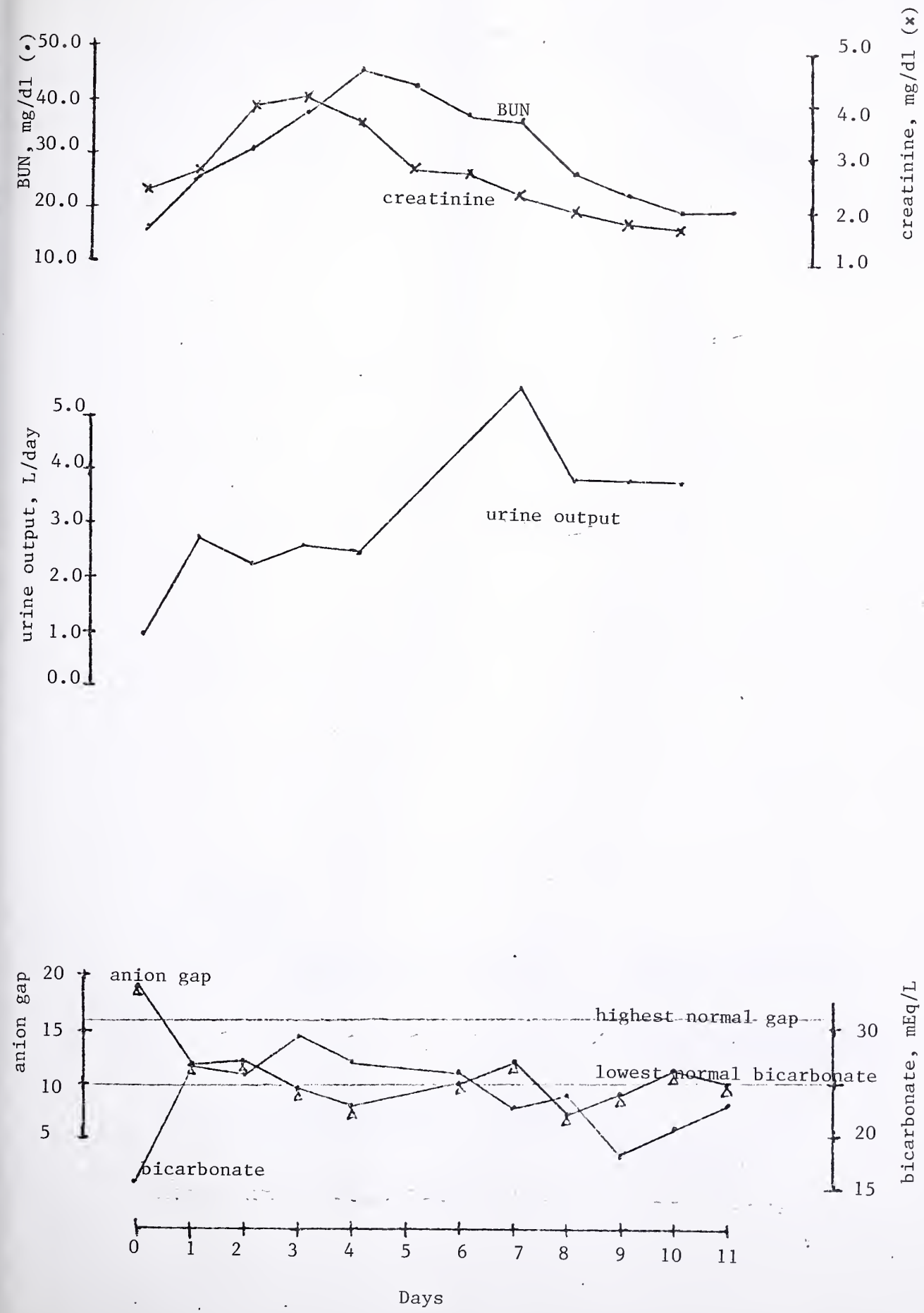

BUN, mg/dl (•)
50.0
40.0
30.0
20.0
10.0
BUN
creatinine
5.0
4.0
3.0
2.0
1.0
creatinine, mg/dl (×)
urine output, L/day
5.0
4.0
3.0
2.0
1.0
0.0
urine output
anion gap
20
15
10
5
anion gap
highest normal gap
lowest normal bicarbonate
bicarbonate
30
20
15
bicarbonate, mEq/L
0
1
2
3
4
5
6
7
8
9
10
11
Days

FIGURE 4: EC

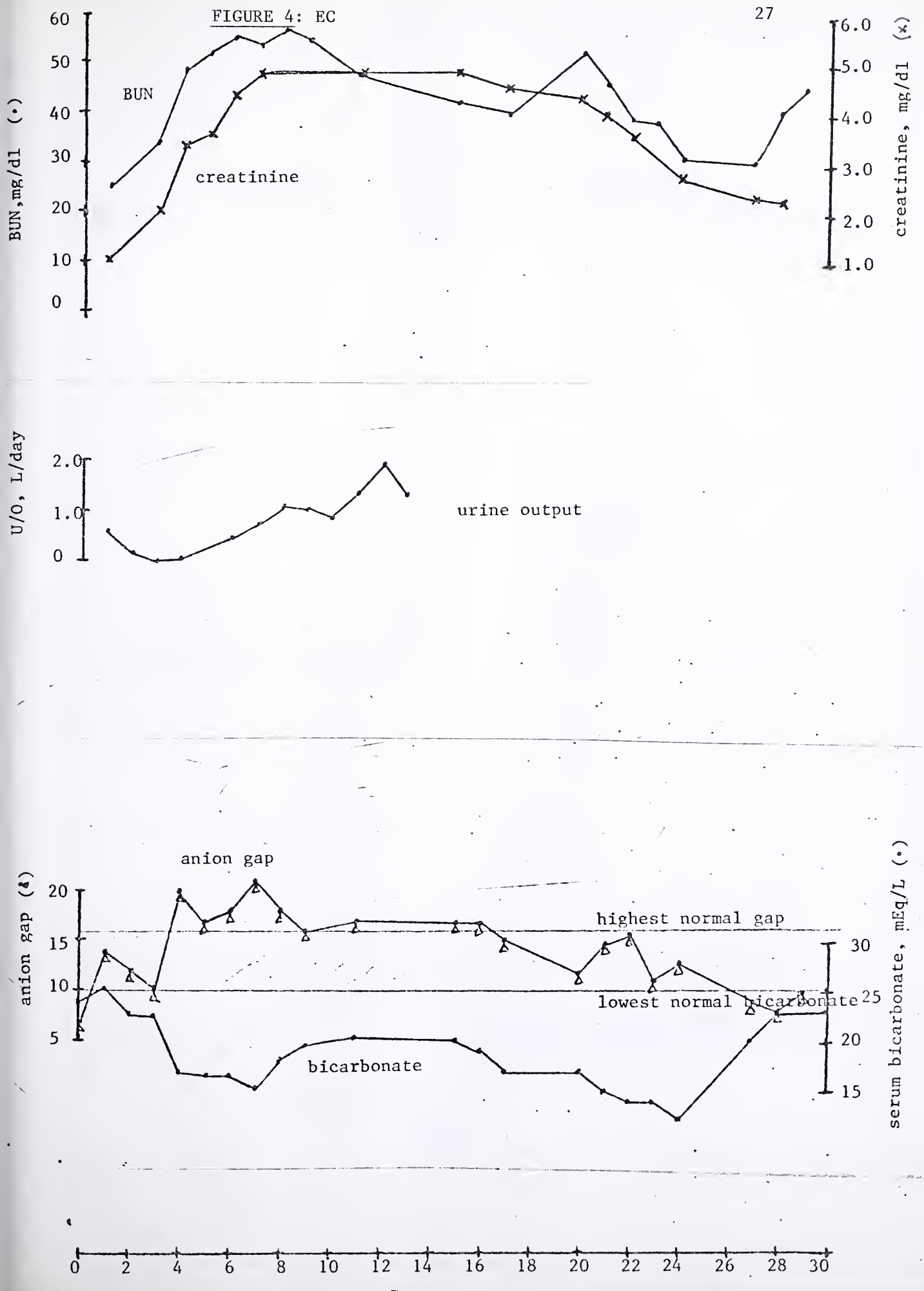

BUN, mg/dl (•)
60
50
40
30
20
10
0
BUN
creatinine
6.0
5.0
4.0
3.0
2.0
1.0
creatinine, mg/dl (×)
U/O, L/day
2.0
1.0
0
urine output
anion gap (%)
anion gap
20
15
10
5
highest normal gap
lowest normal bicarbonate
bicarbonate
30
25
20
15
serum bicarbonate, mEq/L (•)
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Days

FIGURE 5: WD

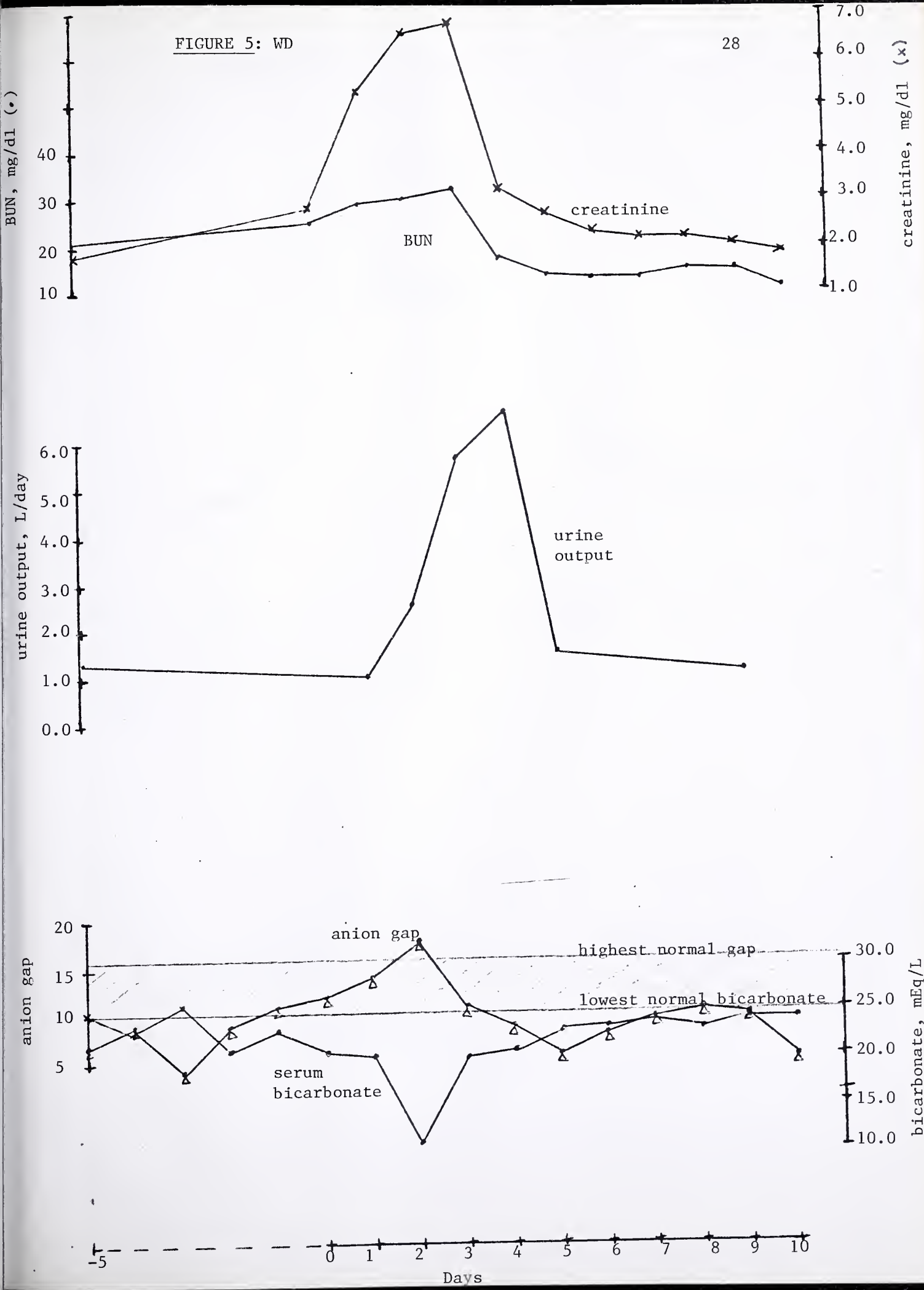

BUN, mg/dl (•)
40
30
20
10
creatinine, mg/dl (×)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
creatinine
BUN
urine output, L/day
6.0
5.0
4.0
3.0
2.0
1.0
0.0
urine output
anion gap
20
15
10
5
anion gap
highest normal gap
lowest normal bicarbonate
serum bicarbonate
30.0
25.0
20.0
15.0
10.0
bicarbonate, mEq/L
-5
0
1
2
3
4
5
6
7
8
9
10
Days

FIGURE 6: RG

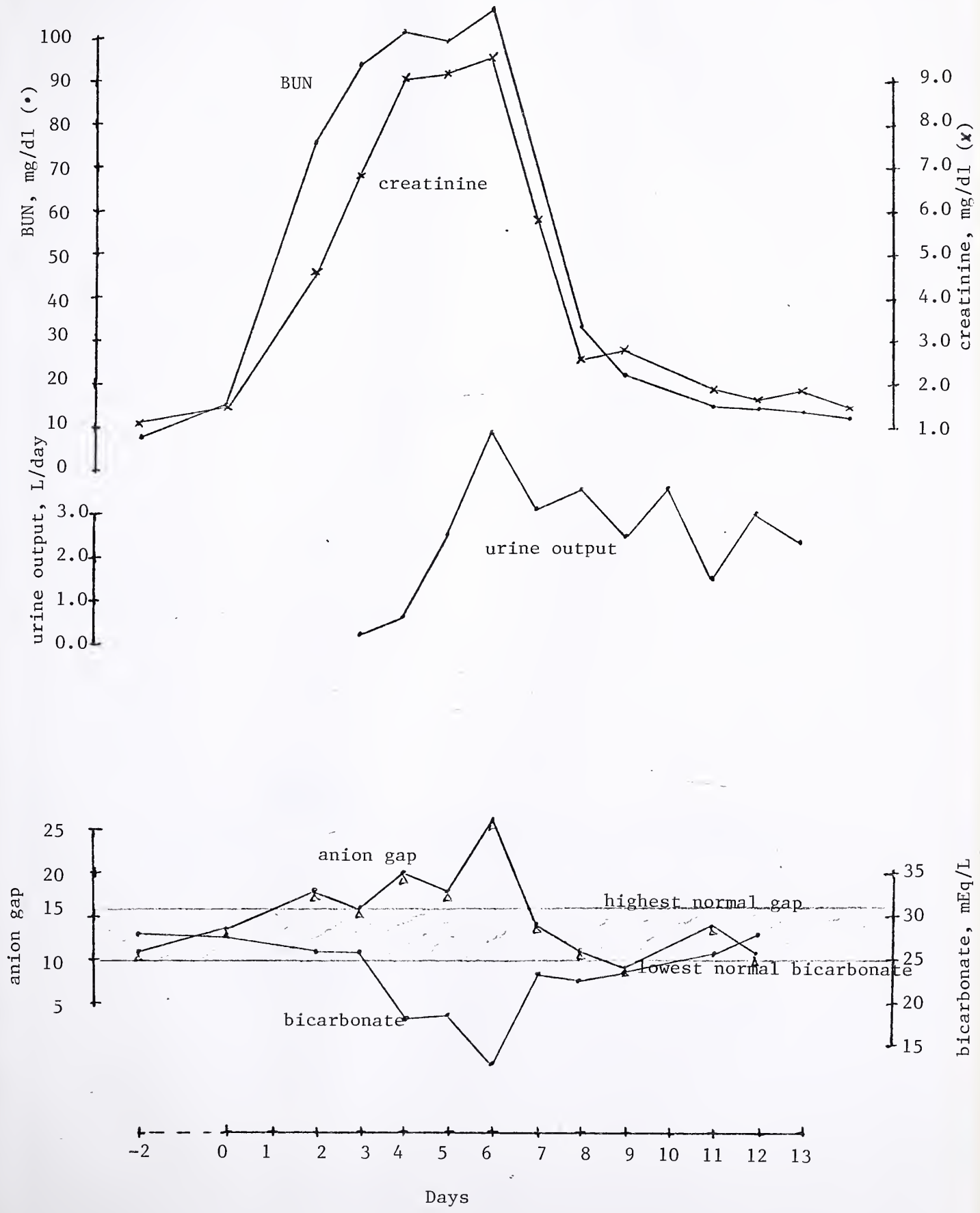
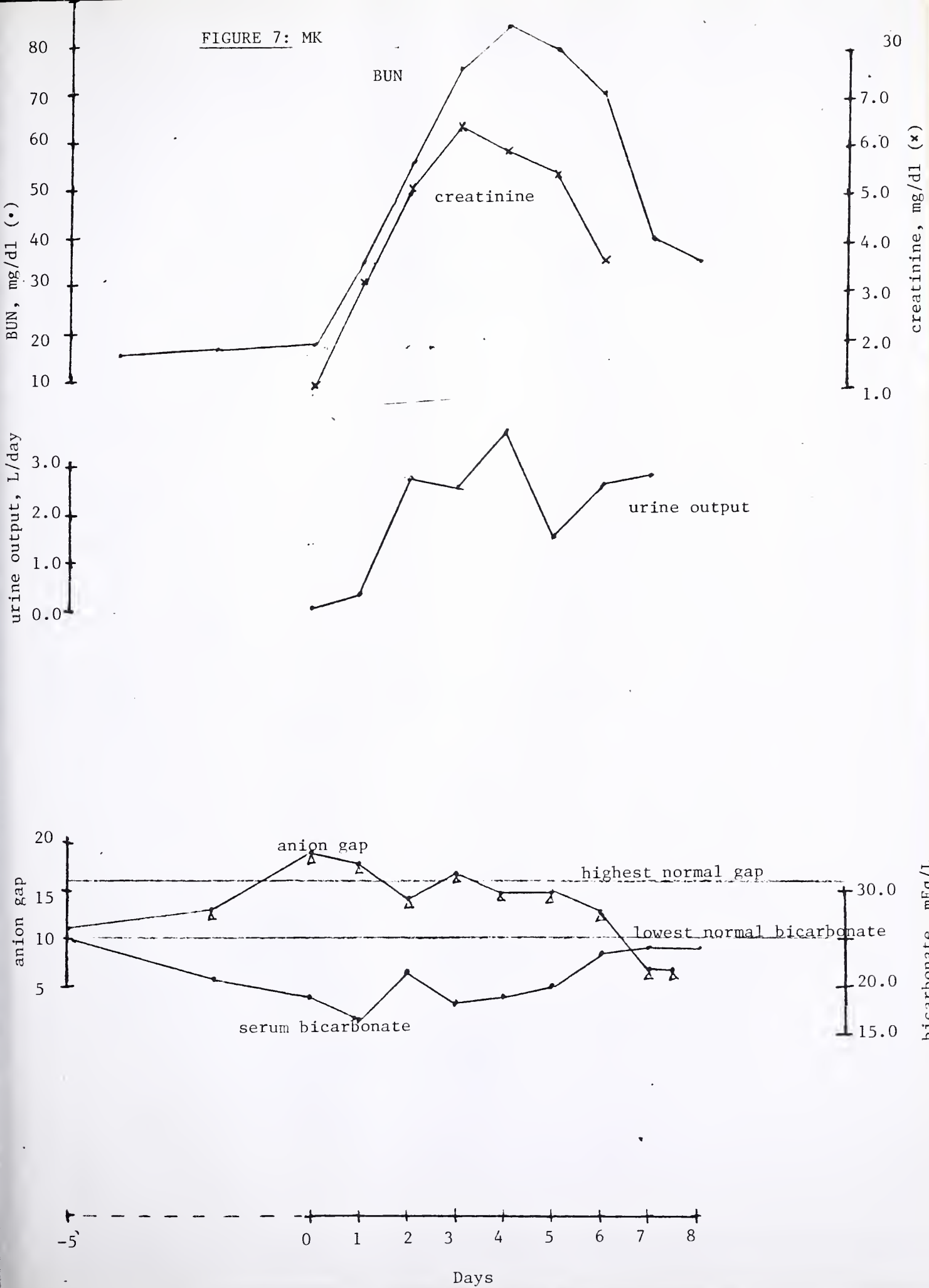

BUN, mg/dl (•)
100
90
80
70
60
50
40
30
20
10
0
BUN
creatinine
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
creatinine, mg/dl (×)
urine output, L/day
3.0
2.0
1.0
0.0
urine output
anion gap
25
20
15
10
5
anion gap
highest normal gap
lowest normal bicarbonate
bicarbonate
35
30
25
20
15
bicarbonate, mEq/L
-2
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Days

FIGURE 7: MK


BUN
creatinine
BUN, mg/dl (•)
creatinine, mg/dl (×)
80
70
60
50
40
30
20
10
30
7.0
6.0
5.0
4.0
3.0
2.0
1.0
urine output
urine output, L/day
3.0
2.0
1.0
0.0
anion gap
highest normal gap
lowest normal bicarbonate
serum bicarbonate
anion gap
bicarbonate, mEq/L
20
15
10
5
30.0
20.0
15.0
-5
0
1
2
3
4
5
6
7
8
Days

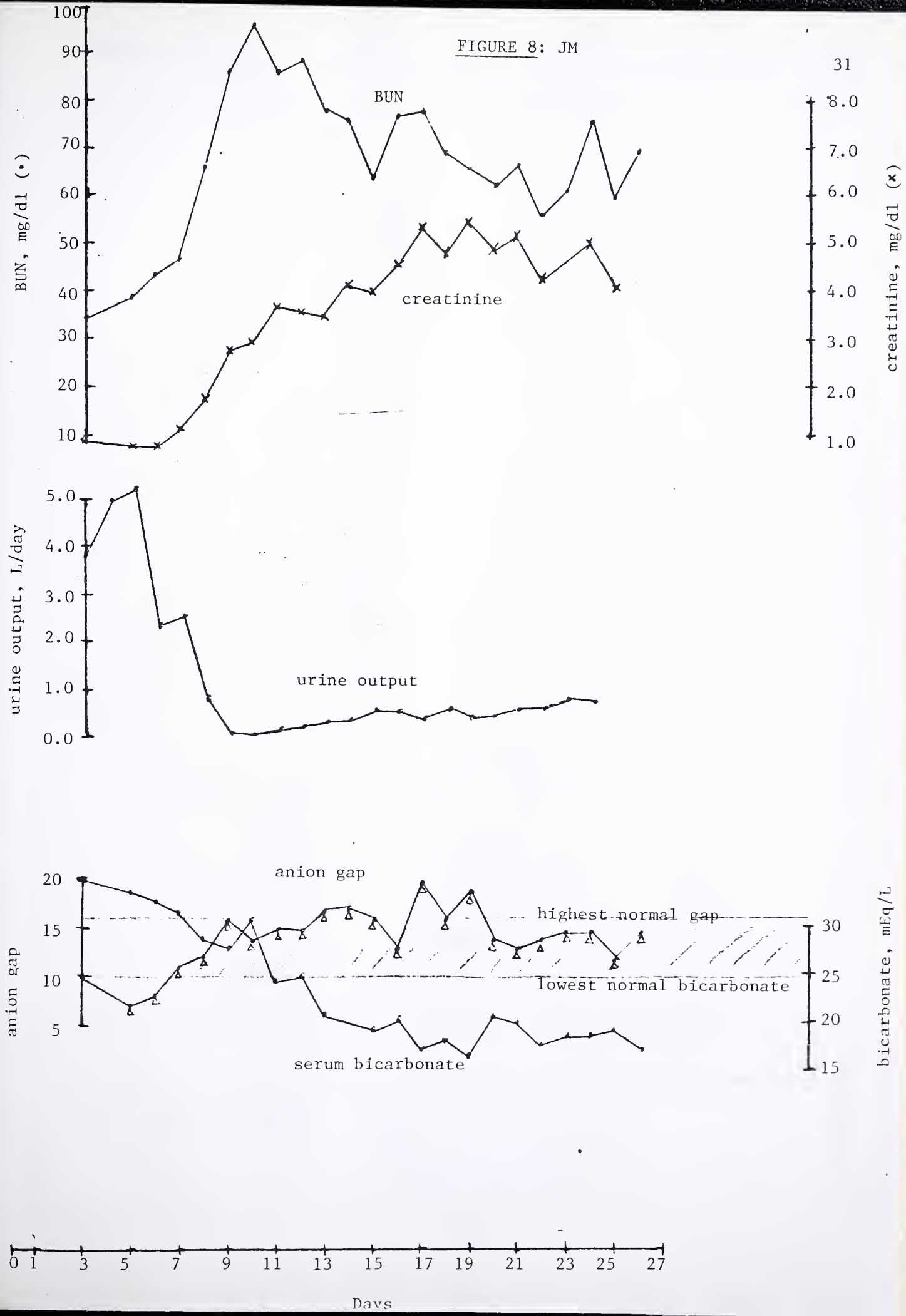


FIGURE 8: JM
BUN
creatinine
BUN, mg/dl (•)
creatinine, mg/dl (×)
urine output
urine output, L/day
anion gap
highest normal gap
lowest normal bicarbonate
serum bicarbonate
bicarbonate, mEq/L
Days

FIGURE 9: IP

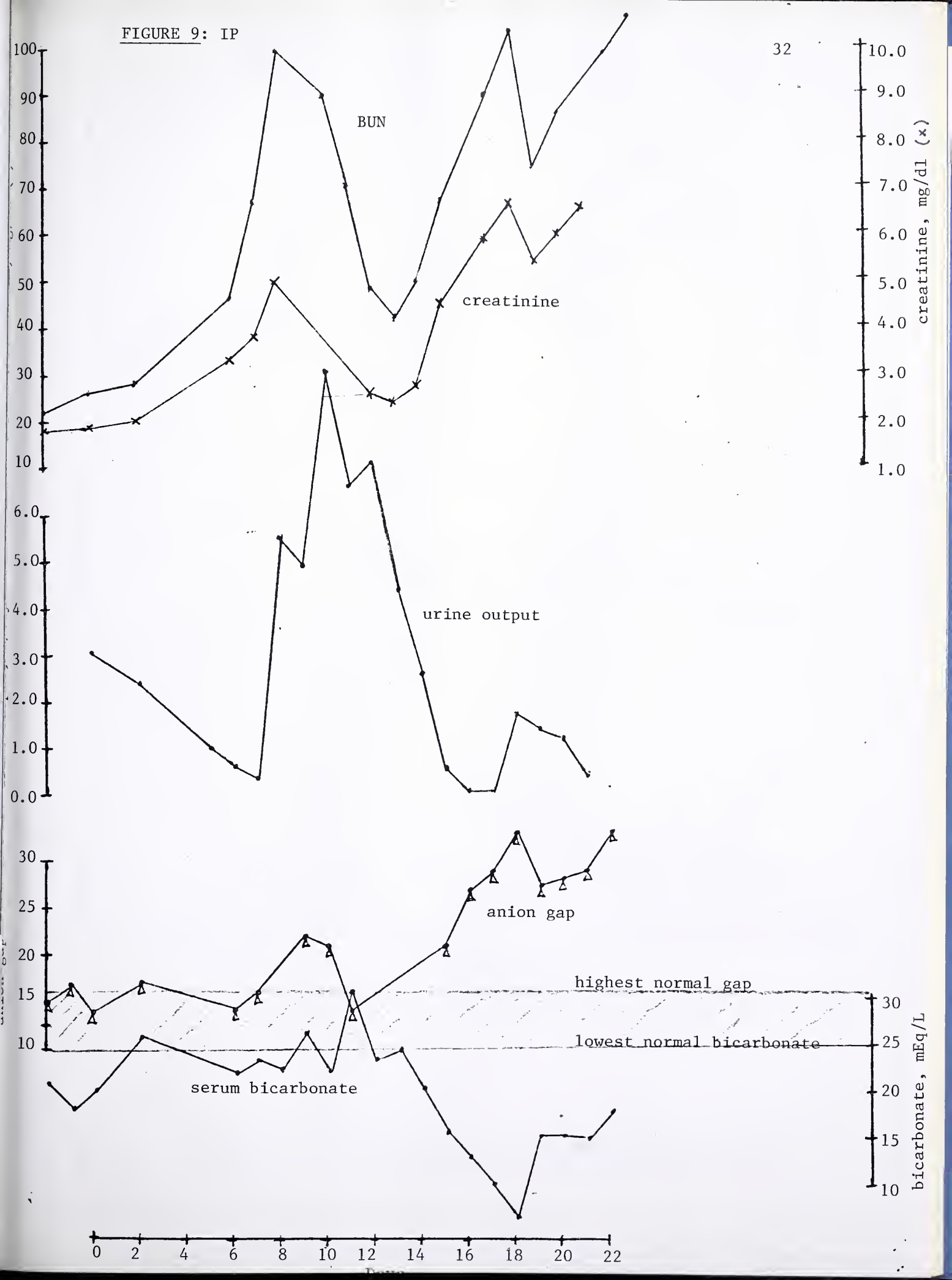

BUN
creatinine
creatinine, mg/dl (×)
urine output
anion gap
highest normal gap
lowest normal bicarbonate
serum bicarbonate
bicarbonate, mEq/L
Days

FIGURE 10: CP

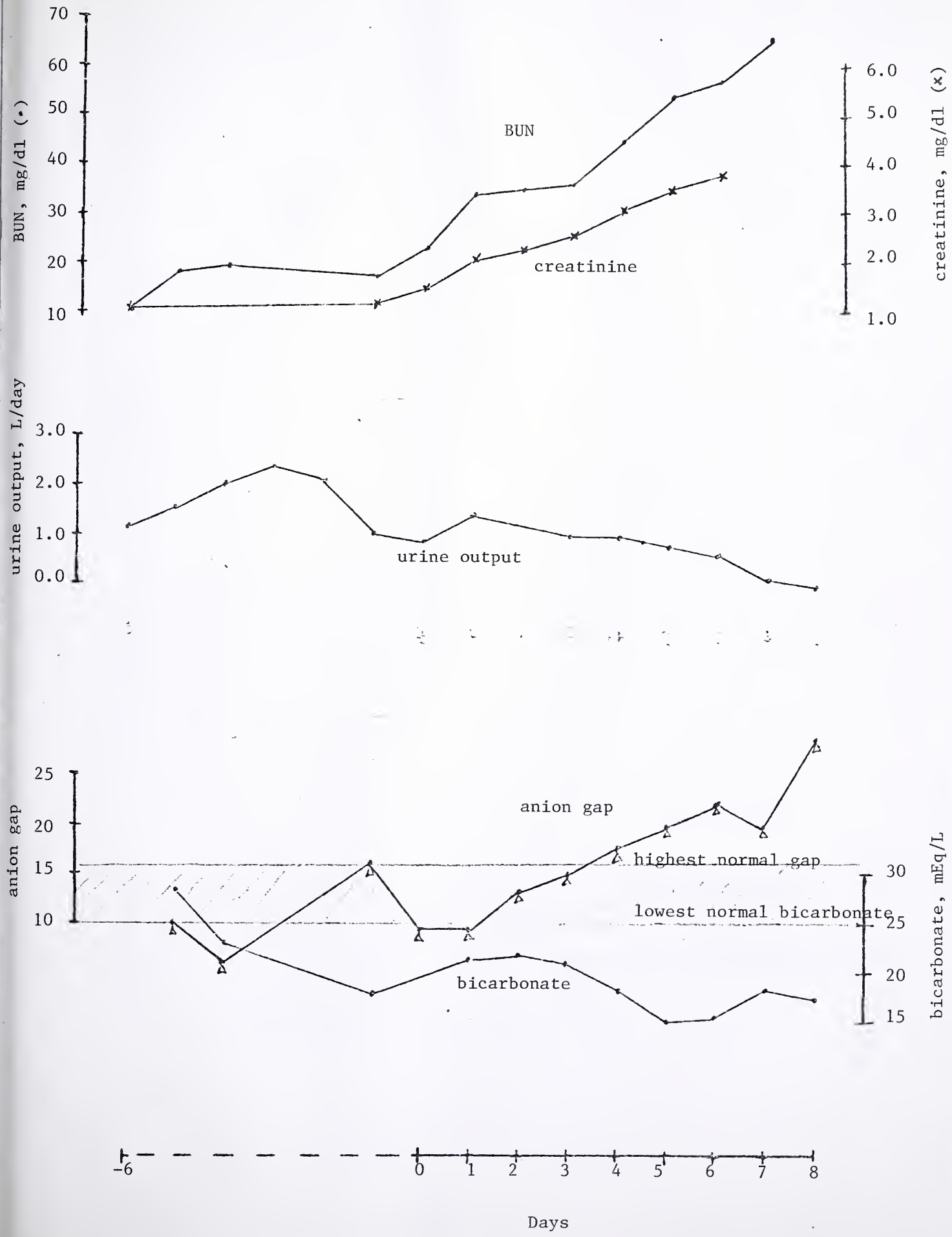

BUN, mg/dl (•)
70
60
50
40
30
20
10
BUN
creatinine
6.0
5.0
4.0
3.0
2.0
1.0
creatinine, mg/dl (×)
urine output, L/day
3.0
2.0
1.0
0.0
urine output
anion gap
25
20
15
10
anion gap
highest normal gap
lowest normal bicarbonate
bicarbonate
30
25
20
15
bicarbonate, mEq/L
-6
0
1
2
3
4
5
6
7
8
Days

FIGURE 11 :LP

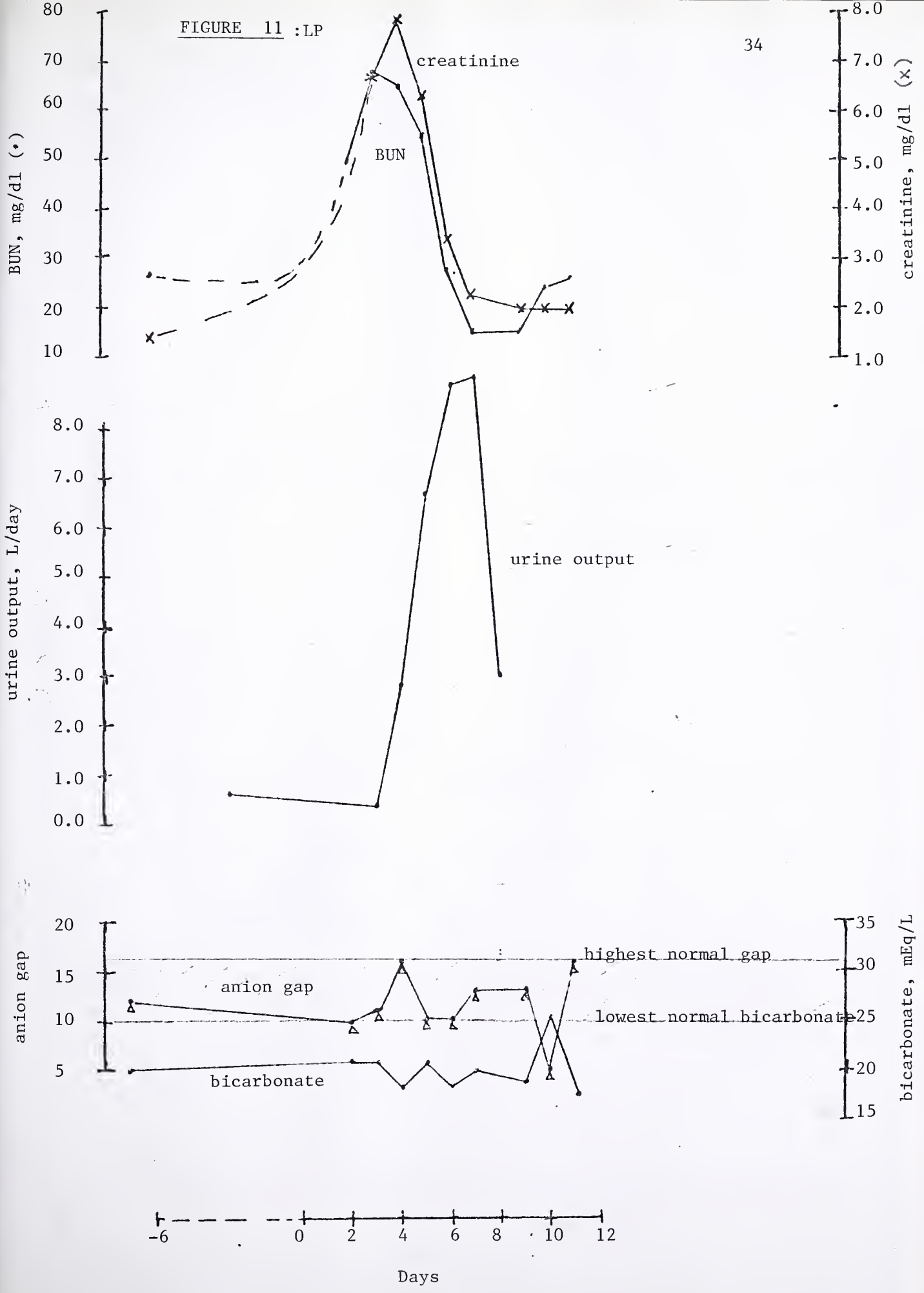

BUN, mg/dl (•)
creatinine, mg/dl (×)
creatinine
BUN
urine output, L/day
urine output
anion gap
highest normal gap
lowest normal bicarbonate
bicarbonate
bicarbonate, mEq/L
Days

FIGURE 12: MS

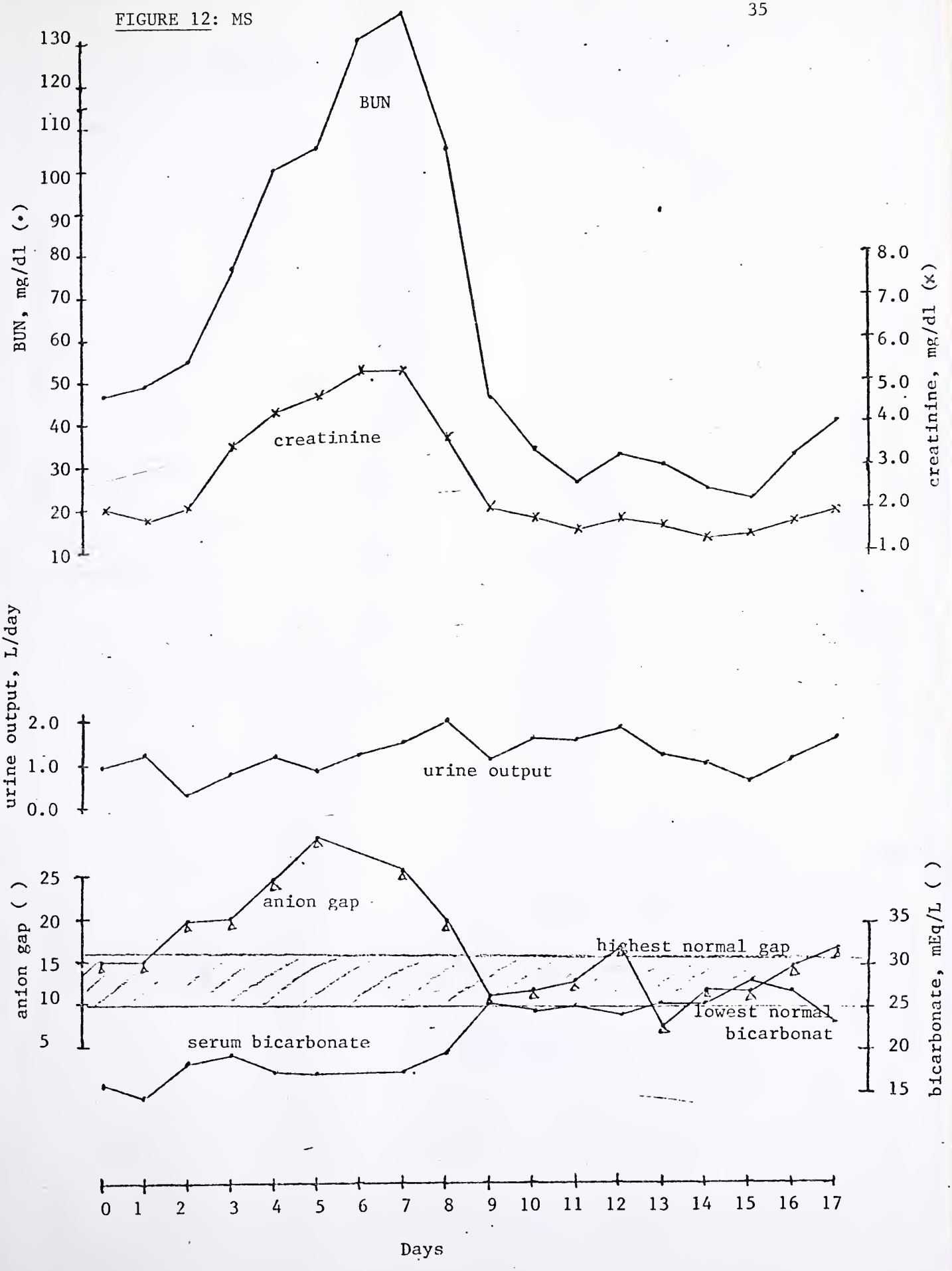

BUN
creatinine
BUN, mg/dl (•)
creatinine, mg/dl (×)
130
120
110
100
90
80
70
60
50
40
30
20
10
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
urine output
urine output, L/day
2.0
1.0
0.0
anion gap
serum bicarbonate
highest normal gap
lowest normal
bicarbonat
anion gap ( )
bicarbonate, mEq/L ( )
25
20
15
10
5
35
30
25
20
15
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Days

FIGURE 13 : WW

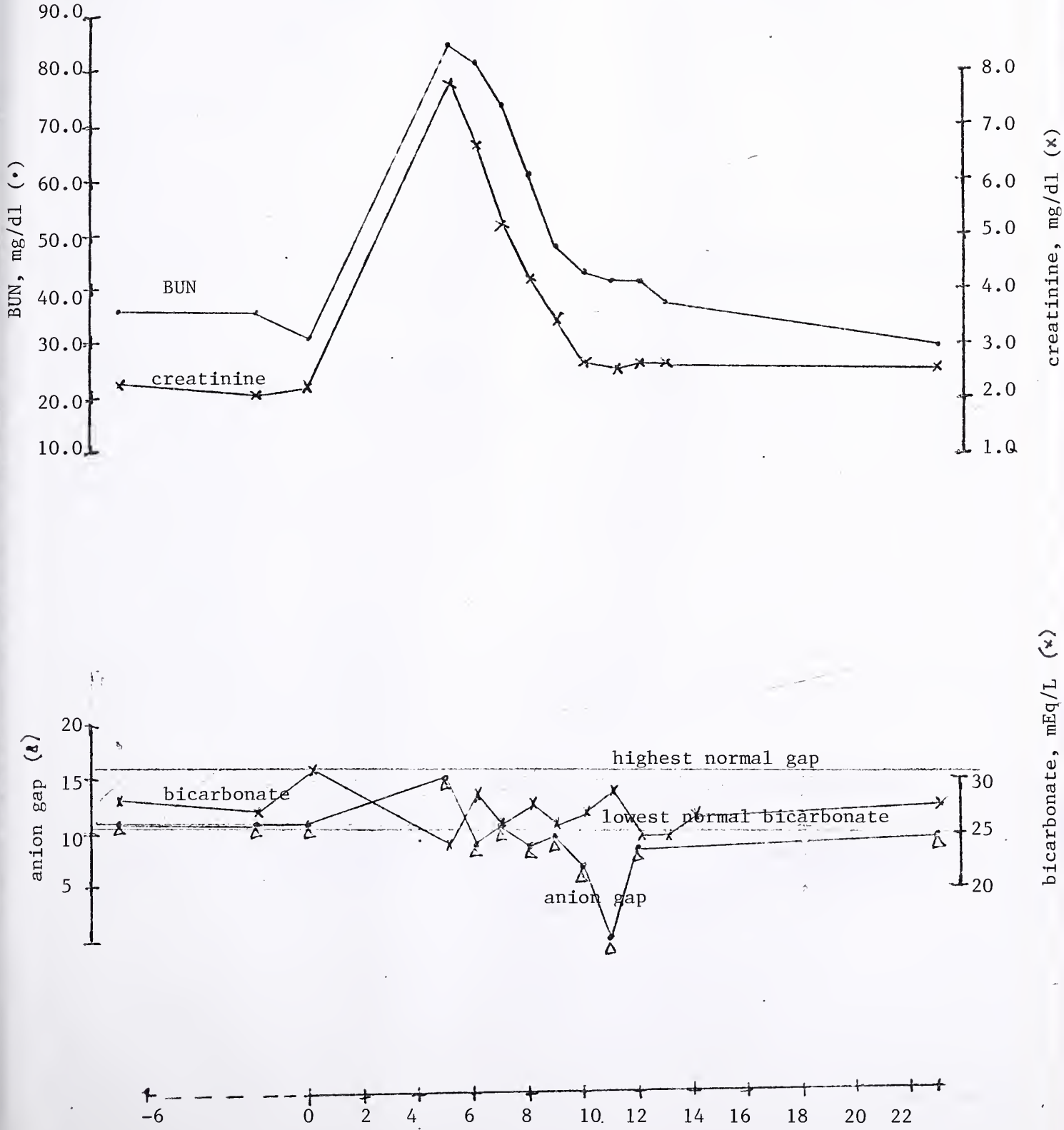
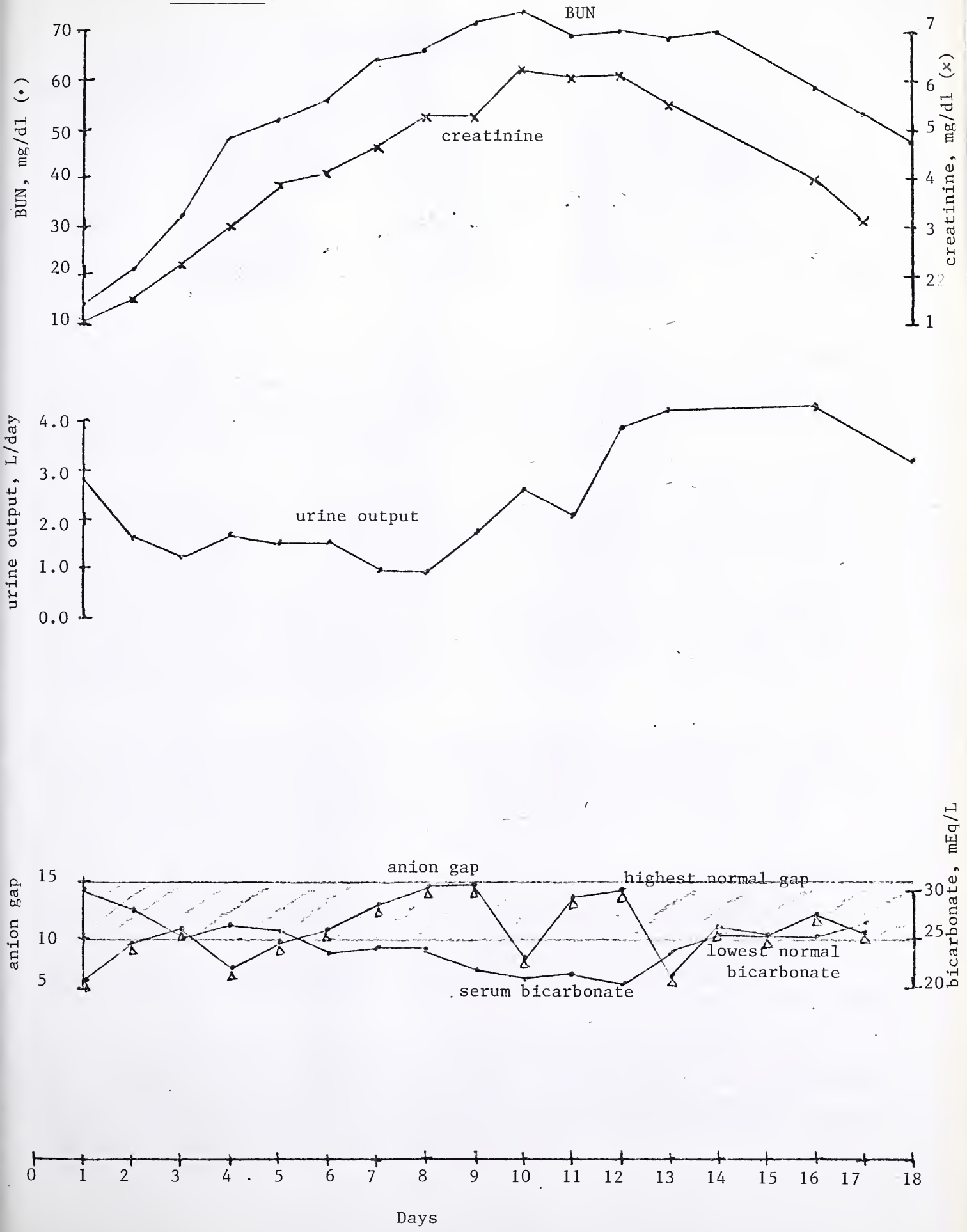

90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
BUN, mg/dl (•)
BUN
creatinine
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
creatinine, mg/dl (×)
20
15
10
5
anion gap (Δ)
highest normal gap
bicarbonate
lowest normal bicarbonate
anion gap
30
25
20
bicarbonate, mEq/L (×)
-6
0
2
4
6
8
10
12
14
16
18
20
22
Days

FIGURE 14: HW


BUN
creatinine
BUN, mg/dl (•)
creatinine, mg/dl (x)
70
60
50
40
30
20
10
7
6
5
4
3
2
1
urine output
urine output, L/day
4.0
3.0
2.0
1.0
0.0
anion gap
highest normal gap
lowest normal bicarbonate
serum bicarbonate
anion gap
bicarbonate, mEq/L
15
10
5
30
25
20
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Days

MEDICAL SUMMARIES

Additional Abbreviations, this section:

ABG	arterial blood gas	MI	myocardial infartion
BC	blood culture	MVA	motor vehicle accident
D/C	discontinuation	NG	nasogastric suction
ER	emergency room	PD	peritoneal dialysis
Gent	Gentamycin	Post-op	post- operative
HCO_3^-	bicarbonate	pt.	patient
HD	hemodialysis	PTA	prior to admission
HTN	hypertension	Tobra	Tobramycin
IV	intravenous	y.o.	years old

TB: 79 y.o. ♂ brought to ER on Day 0 with cyanosis and hypotension, progressing to cardiac arrest. Some degree of renal insufficiency noted PTA, but normal kidneys viewed on ultrasound. Pt. continued with low cardiac output and progressive oliguria until he expired on Day 8 from cardiac failure. He was acidemic on Day 0 and 1, but thereafter pH's ranged 7.43-7.55.

SB: 32 y.o. ♀ suicide attempt by ingestion of ½ glass ethylene glycol 10 days PTA (Day 0), with onset of oliguria and vomiting 2 days PTA. Pt. was anuric the first 5 days of admission, and PD was begun on admission and continued for 20 days. Fluid changes were poorly tolerated with associated HTN, psychotic symptoms, and two grand mal seizures on Day 18. This was followed by aspiration pneumonia and acute respiratory distress syndrome requiring intubation through Day 31. After D/C of PD, pt. required IV HCO_3^- on Day 34 for acidemia of pH 7.31. On Day 39 regular oral doses of HCO_3^- were begun and continued for blood pH's of 7.28, 7.29, 7.31 (Days 39,43,48, respectively), during which time the patient was symptomatic only with nausea and pruritis. On Day 48 the pt. was transferred to the psychiatric ward.

WB: 37 y.o. ♂ suicide attempt by intracardiac stab wound < 12 hours PTA (Day 0). Pt. arrived in ER hypotensive and was taken to surgery for plication of right ventricular wound with insertion of chest tubes for hemopericardium. He required 13 liters of fluids intraoperatively and experienced post-op bleeding. The rest of hospital course was uncomplicated, with full recovery. The pt. was acidemic Days 0,1, and thereafter pH's ranged 7.42-7.58.

EC: 85 y.o. ♀ admitted 3 months prior to onset of ATN for altered mental status proven to be brain reticulum cell sarcoma. Pt. developed enterococcal sepsis on Day -11 and was started on Gent. On Day 2 she developed oliguria and Gent was D/C'd on Day 3. Pt. had significant NG losses on Days 1,6,7. The remainder of the course was complicated by a urinary tract infection and altered mental status. Her pH remained alkaline throughout the ATN, ranging 7.44-7.54. She was discharged after moderate recovery of renal function, terminal with sarcoma.

WD: 87 y.o. ♂ admitted 1 month prior to ATN for syncope and abdominal pain, later proven to be acute cholecystitis. He was begun on Gent on Day -3. On Day 1 his surgery was cancelled because of ARF. No other history of nephrotoxins was available, and all other etiologies of ARF and ATN were excluded. He recovered and was transferred to the surgical service for cholocystectomy. ABG's were drawn on Days 1,2 only, and revealed normal pH.

RG: 24 y.o. ♂ IV drug abuser admitted Day 4 of ATN (hospital transfer) with bacterial endocarditis of the tricuspid valve and right-sided empyema secondary to septic embolus. Although urinary indices were indeterminate in this pt., the radiographic and lab data as well as course were felt to be consistent with ATN. The pt. had been hypotensive and received 2 days of Gent and Indomethacin PTA, and with a known focus of infection, multiple insults (↓BP,sepsis,Gent) inciting ATN had to be invoked. The only ABG obtained was on Day 6, with a normal pH. Following recovery of renal function the patient was transferred for thoracic surgery.

MK: 67 y.o. ♀ admitted Day -11 with probable MI. On Day 0 she had a cardiopulmonary arrest and was resucitated. She then required norepinephrine, dopamine, and intra-aortic balloon placement for maintainence of BP. Arrhythmias and bradycardia continued with further hypotension on Day 4. The patient was cardioverted on Days 6,7,8, and expired on Day 8 with asystole. Blood pH's were in the normal range.

JM: 77 y.o. ♂ admitted 1 month prior to ATN for trauma incurred in MVA. Initial post-op recovery was complicated by the development of an infected perihepatic hematoma, with onset of fever on Day -5, followed by hypotension on Day 0 requiring emergency surgical drainage. On Day 5 Tobra was D/C'd after a total course of 21 days. Post-op complications included coma and candidal sepsis, starting Day 6, biliary fistula, and staphylococcal pneumonia starting Day 18. HD was begun on Day 6 and continued three times weekly throughout. The pt. remained septic and expired on Day 27. The only documented acidemia was on Day 9 with pH's 7.32-7.35.

IP: 66 y.o. ♀ admitted with acute abdomen on Day 0 requiring hemicolectomy for bowel infarction and perforation. Post-op complications included sepsis, development of oliguria on Day 4, pancreatitis on Day 13, continuation of sepsis with WBC=45,000, but BC's (-), development of heart block on Day 14, and HTN and anemia. HD was performed once on Day 18, and on Day 21 pericardial rub, tremors, and disseminated intravascular coagulation began. The pt. expired on Day 23. Antibiotics had been given as follows: Gent for 11 days, Carbenicillin for 12 days, with 2 days overlap between the two, and a peak Gent blood level of 19 on Day 13. Documented acidemia occurred on Days 6,7,16,17, and 22, with pH's 7.37,7.35,7.37,7.26, and 7.30 respectively.

CP: 62 y.o. ♂ admitted 2½ weeks prior to onset of ATN with bowel transection incurred in MVA. Initial post-op recovery was fair, and 2 weeks post-op there were persistent fevers and (+) cultures from sputum, abdomen, and colostomy. On Day 1 septic shock necesitated reexploration, revealing no abscess, but 1 liter of peritoneal fluid culture (+) staphylococcus. On Day 7 respiratory failure began, and the pt. expired on Day 8 following generalized seizures. Gent was given for 19 days total, and Tobra for 5 days, with no overlap. Acidemia was documented on Days 1,8 with pH's 7.33, 7.31 respectively.

LP: 52 y.o. ♀ with insulin-dependent diabetes and atherosclerotic vascular disease was admitted electively on Day -5 for workup of angina. Pt. underwent cardiac catheterization on Day -5 with 145 cc. dye injection and tolerated the procedure well. On Day 0 digital angiography was performed with 130 cc. dye, followed the next day by abdominal CT scan with contrast media. No episodes of hypotension or hypovolemia were noted prior to the onset of ATN. The rest of the hospital course was remarkable only for a brisk diuresis. No ABG's were obtained on this patient.

MS: 47 y.o. ♀ with primary biliary cirrhosis and rheumatoid arthritis, on Prednisone, was admitted on Day 0 with legionella pneumonia, coagulopathy, and dehydration. Admission labs included WBC=19,000 and PaO_2=41, requiring intubation. Legionella was (+) on smear and culture. The pt. was rehydrated, but nonetheless experienced hypotension on Days 0,1,2. She deteriorated progressively with rising fevers despite treatment with Erythromycin and Rifampin for legionella, and developed oliguria on Day 2 while euvolemic by intravascular pressures and peripheral perfusion. On Day 6 sputum cultures grew yeast, and by Day 7 WBC had risen to 29,000, and a pericardial rub was noted. PD was begun and continued through Day 13. By Day 14 skin, urine, and peritoneal cultures all grew yeast. The pt. continuously deteriorated, with respiratory insufficiency and sepsis clinically, though cultures eventually all became (-). Later in the hospital course renal decompensation recurred (Day 26), reaching BUN 99 and creatinine 4.9 on Day 30, and the pt. finally expired on Day 32. The pt. was frequently acidemic throughout the study, with pH's $\leq$ 7.37 on nine of the days between Day 4-15. She was given HCO_3^- on Days 0,1.

WW: 66 y.o. ♂ status-post post prostatectomy for Adenocarcinoma, on DES therapy, was admitted on Day -1 for workup of abdominal pain and leg swelling. The pt. had one functioning kidney (by IVP and retrograde cystoscopy 2 months PTA, and by renal scan this admission), and the right kidney was shown non-functioning with distortion of the ureter by mass. On Day 0 an inferior venacavagram was performed with 190 cc. of dye injection, and was well-tolerated. When ARF ensued a renal scan was done, showing good blood flow to the left kidney, and retrograde cysoscopy revealed no ureteric obstruction on the left. The course of the ATN was uneventful, and the pt. later developed other complications related to his malignancy. There was no documentation of ABG's or urinary output during the study.

HW: 63 y.o. ♂ admitted Day -12 for injuries incurred in MVA including major facial trauma, flail chest, splenic laceration, and extremity injuries. Initial post-op recovery was good, but fevers began on Day -5 and continued through Day 1. Hypotension occured on Day -1, and dopamine was D/C'd on Day 0. Although hypotension could not be clearly excluded, it was felt that aminoglycoside nephrotoxicity was the most likely etiology of the ATN, considering timing and pattern of onset. Gent was given for a total of 3 days, and Tobra for 10 days (D/C'd Day 2), with no overlap of days.

TABLE I. ARF PATIENT BREAKDOWN BY CATEGORY, WITH AGE, PRIMARY DIAGNOSIS, FINAL OUTCOME, AND DAYS INCLUDED IN THE STUDY (ATN PATIENTS)

ARF CATEGORY[1]	PATIENT	AGE	PRIMARY DIAGNOSIS[2]	OUTCOME[3]	DAYS IN STUDY[4]
Prerenal	EH	87	protein-losing nephropathy	recovery	
	EI	51	volume depletion, respiratory decomp.	recovery	
	EL	86	cardiac failure	death	
	EDM	62	pancreatitis	recovery	
Postrenal	EM	72	pelvic tumor	D/C,terminal	
Vascular	SW	44	solitary kidney, thrombosis of renal artery	CRF	
ATN	TB	79	cardiac failure	death	4-6
	SB	32	ethylene glycol ingestion	recovery	10-48
	WB	37	stab wound	recovery	4-10
	EC	85	brain tumor	D/C,terminal	7-15
	WD	87	cholecystitis	recovery	8-12
	RG	24	endocarditis	recovery	4-6
	MK	67	cardiac failure	death	8
	JM	77	trauma (MVA), infection	death	9-24
	IP	61	bowel infarcton	death	9-24
	CP	60	trauma (MVA)	death	7-8
	LP	52	atherosclerosis, diabetes	recovery	4-9
	MS	47	pneumonia, primary biliary cirrhosis	death	4-15
	WW	66	retroperitoneal lymphoma	recovery, terminal	9-13
	HW	63	trauma (MVA)	recovery	5-18

TABLE I. Footnotes

[1] categories determined as outlined in Introduction, pages 1-3.

[2] primary diagnosis for hospitalization, and secondary diagnoses where related to renal failure

[3] outcome of illness, as documented by last entry in medical record, defined:
recovery = return of baseline renal function
D/C = discharge from hospital after improved renal function
terminal = discharge with expectation of death

[4] days after ATN insult on which samples were collected for this study, with Day 0 defined as the day of the insult, numbered days corresponding to days graphed (Figures 1-14)

TABLE II. ATN PATIENT INSULTS, PATIENT NUMBERS, AGES, AND MORTALITIES

INSULT	NUMBER PATIENTS (ID)	AGE,AV. (RANGE)	MORTALITY
NEPHROTOXIC			
- Radiographic Dye	2 (LP,WW)	59 (52-66)	0%
- Aminoglycosides	3 (EC,WD,HW)	78 (63-87)	0%
- Organic Solvent	1 (SB)	32	0%
POST-ISCHEMIC			
Hypotension	3 (TB,WB,MK)	61 (37-79)	67%
MULTIPLE INSULTS			
Hypotension/Sepsis/ Aminoglycosides	5 (IP,CP,JM,RG,MS)	54 (24-77)	80%
OVERALL	14	60 (24-85)	43%

TABLE III. URINARY INDICES IN ATN PATIENTS

PATIENT	Fe_{Na}	U_{Na}	U/P creat	U/P osmo	RFI	DAY [1]	
TB	2.2	22	7.2	1.1	3.1	3	
SB	17.8	78	3.2		24.4	24	
WB	0.6	26	30.3	1.7	0.9	5	
EC	1.5	30	16.5	1.0	1.8	3	
WD		78				10	
RG		55		1.2		9	
MK		88		1.0		3	
JM			8.5			18	
		38		0.9		20	
IP	45	108	1.7		63.5	22	
CP				1.0		1	
LP		79		0.7		7	
MS	0.4	10	15.5	1.2	0.6	7	
HW		30		0.6		3	
	6	12	7	10	6		total #
	14.6	54	11.8	1.0	20.3	10	Average
	4 (67%)	6 (50%)	6 (86%)	9 (90%)	4 (67%)		'typical' [2]

[1] the day of ATN listed values were obtained (corresponds to days graphed, Figures 1-14)

[2] 'typical' urinary indices in ATN, defined as: $Fe_{Na} \geq 1\%$, $U_{Na} > 40$, U/P creat < 20, U/P osmo ≤ 1.2, RFI > 1

TABLE IV. FORMED ELEMENTS IN THE URINARY SEDIMENT OF ARF: COMPARISON OF ATN vs. OTHER DIAGNOSTIC CATEGORIES

	PATIENT	DBGC (a/N)[1]	RTC (b/N)[2]	'BENIGN'(c/N)[3]
I. ATN patients				
	TB		X (1/3)	
	SB	X (4/13)	X (5/13)	
	WB	X (7/8)	X (6/8)	
	EC	X (4/7)		
	WD			X (4/4)
	RG			X (2/2)
	MK	X (1/1)		
	JM		X (3/6)	
	IP	X (2/8)	X (6/8)	
	CP			X (3/3)
	LP			X (4/4)
	MS	X (6/7)	X (3/7)	
	WW			X (3/3)
	HW	X (10/19)	X (6/19)	
total # :	14	7	7	5
% of group:		50%	50%	36%
II. OTHER ARF patients				
prerenal	EH	X (2/2)	X (2/2)	
	EI			X (3/3)
	EL	X (3/4)		
	EdM	X (1/2)		
postrenal	EM		X (1/2)	
vascular	SW	X (1/4)		
total #:	6	4	2	1
% of group:		67%	33%	17%

[1] DBGC = dirty brown granular casts
a = number of samples where ≥ 3 casts per slide present
N = total number of sediment samples examined per patient throughout study

[2] RTC = renal tubular cells
b = number of samples where ≥ 3 cells per slide present

[3] 'Benign' = neither DBGC nor RTC present on slide, or if seen, < 3 per slide
c = number of samples examined found to be 'Benign'

TABLE V. PRIMARY ACID-BASE DISTURBANCES IN ATN PATIENTS

OVERALL DISTURBANCE [1]	PATIENTS	EXCEPTIONS, COMPLICATIONS / DAYS [2]
I. mixed metabolic acidosis and respiratory alkalosis	JM	
	IP	pure metabolic acid / 6-8,16,17
	EC	NG losses 300-500 cc per day /2,6,7
	MK	NG losses 100-150 cc per day /0,1,3,5
	MS	respiratory acidosis / 11
	HW	NG loss 235 cc / 11
II. respiratory alkalosis	TB	cardiogenic shock (?lactic acid)/ 0 NG losses 300-470 cc per day / 4-6
	WB	hemorrhagic shock (?lactic acid)/ 0 NG losses / 0-3
	RG	
III. metabolic acidosis	SB	seizures (?lactic acid) /18
	CP	NG losses $\geq$1000 cc per day / 3-6
	11	patients total (with blood gases)

[1] a) primary disturbances of individual blood gases determined by:

1. application of formulas (Data Analysis) to define maximal limits of compensation
2. history of interventions possibly causing metabolic alkalosis
3. determination of mixed disturbance if actual values exceed predicted limits of compensation

b) overall disturbances defined as average of individual blood gas interpretations, excluding days with possible confounding acid-base interventions, as listed above, and excluding dialysis days

c) individual and overall analyses confirmed by Dr.M.Bia

[2] days on which medical or therapeutic course may have altered the primary acid-base disturbance, e.g., dialysis or NG loss causing alkalosis, or shock causing acidosis on arrival

TABLE VI. POSSIBLE CAUSES OF RESPIRATORY ALKALOSIS AND ANION GAP ELEVATION PRESENT IN ATN PATIENTS

PATIENT	CAUSES-RESPIRATORY ALKALOSIS	CAUSES-HIGH ANION GAP
TB	mechanical hyperventilation, CHF	cardiac shock (lactic acid)
SB	mechanical hyperventilation	ethylene glycol (oxalate), dialyzate (lactate), seizures (lactic acid)
WB	anxiety	blood transfusions (citrate) , dehydration, hemorrhagic shock (lactic acid)
EC	sepsis , brain tumor	septic shock (lactic acid)
RG	pulmonary embolus, sepsis, fever	dehydration, septic shock (lactic acid)
MK	mechanical hyperventilation, CHF	cardiac shock (lactic acid)
JM	mechanical hyperventilation, fever	dialyzate (acetate)
IP	mechanical hyperventilation, sepsis, fever	dialyzate (acetate), carbenicillin anion, blood transfusions (citrate)
CP	mechanical hyperventilation, sepsis, fever	septic shock (lactic acid) blood transfusions (citrate)
MS	mechanical hyperventilation, hepatic insufficiency, pneumonia	dehydration, septic shock (lactic acid)
HW	head trauma, sepsis, mechanical hyperventilation	septic shock (lactic acid)

TABLE VII. URINARY ACIDIFICATION IN ATN

PATIENT	MINIMAL U_{pH} (x/y)[1]	MINIMAL BLOOD pH (N)[2]	DAY[3]
TB	4.80 (3/3)	7.48 (3)	5
SB	5.33 (2/12) 7.28	7.44 (9) 7.35	10 27
WB	5.75 (0/7)	7.42 (4)	7
EC	5.35 (5/7)	7.44 (2)	7
WD	5.22 (2/5)	7.39 (1)	2
RG	5.09 (2/2)	(0)	4
MK	(0)	(0)	
JM	6.30 (2/4)	7.33 (3)	9
IP	5.04 (2/7)	7.37 (4)	9
CP	5.48 (3/3)	7.37 (3)	7
LP	5.20 (2/3)	(0)	8
MS	5.22 (4/7)	7.36 (7)	4
WW	4.90 (2/2)	(0)	9
HW	5.13 (11/16)	7.41 (9)	11
14 total			7.1 ± 2.7 (Av. ± SD)

[1] The value listed is the minimum U_{pH} obtained throughout the study, or the U_{pH} when the blood pH is acidemic.
x = the total number of U_{pH} values = 5.5 obtained per person
y = the total number of measurements done per person throughout the study

[2] Results listed include all blood pH's $\leq$ 7.37 noted during the study with simultaneous U_{pH} result; where no blood pH $\leq$ 7.37 was measured throughout the study for a patient, the value associated with the lowest U_{pH} is listed.
N = total number of blood gas measurements during the study (ordered by housestaff only)

[3] the number of days after the presumed ATN insult that the U_{pH} measurement was obtained (corresponds to days graphed, Figures 1-14)

TABLE VIII. URINARY ACIDIFICATION IN CRF PATIENTS

PATIENT		SERUM BICARBONATE		U_{pH} [1]
PA		13.3		6.72
PC		16.4		7.62
RK		13.6		5.52
RL		17.7		5.40
SM		18.6		7.48
MS		15.8		7.92
DS		19.6		6.25
LS		15.8		6.30
RT		16.5		7.35
WW		19.7		5.39
tal 10	Av±SD	16.7 ± 2.2	Av±SD	6.60 ± 0.97

[1] U_{pH} and serum bicarbonate measurements done prior to dialysis and within two hours of eachother

APPENDIX

OVERALL ACID-BASE DISORDER	PATIENT	pH DISTURBANCES / DAYS [1]
I. mixed metabolic acidosis and respiratory alkalosis	JM	alkalemia / 7,19,20 acidemia / 7,13
	IP	acidemia / 6,7,16,17 alkalemia / 8-11
	EC	
	MK	acidemia / 0,5,6 alkalemia / 1-3
	MS	
	HW	alkalemia / 1-3,6-8,14,17,18
II. respiratory alkalosis	TB	acidemia / 0-1 alkalemia / 2-6
	WB	acidemia / 0-1 alkalemia / 2-9
	RG	
III. metabolic acidosis	SB	alkalemia / 10-23 acidemia / 27-48
	CP	acidemia / 1,7,8

[1] days correspond to those in Figures 1-14; days not listed revealed normal blood pH's, defined as 7.38-7.42, when blood gases were drawn ; alkalemia = pH $\searrow$ 7.42; acidemia = pH $\swarrow$ 7.38

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